PAIR (Paracetamol and Ibuprofen Research) Pilot Trial

Full Title	PAIR (Paracetamol and Ibuprofen Research) Study: A randomised controlled trial comparing IV paracetamol with IV ibuprofen in the management of haemodynamically significant patent ductus arteriosus
Sponsor **Sponsor reference**	Manchester University Foundation NHS Trust B01039
IRAS Number	1003574
EudraCT number	2020-003863-25
Clinical trials.gov number:	TBC
Sponsor reference	B01039

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

This project will be conducted in accordance with the study protocol, Trust SOPs and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki. All individuals will be considered for inclusion in this study regardless of age, disability, race, religion and belief, except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication in medical journals or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:

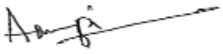
..... Date: ...../...../.....

Name (please print):

.....

Position: .....

Chief Investigator:

Signature:  ..... Date: 16 / 06 / 2021.

Name: (please print):

.....(Dr Arindam Mukherjee) .....

KEY TRIAL CONTACTS

Chief Investigator	Dr Arindam Mukherjee Saint Mary's Hospital Manchester University NHS Foundation Trust
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Committees	Trial Steering Committee Members: 1. Dr Abhijeet Godhamgaonkar, Clinical lead, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT 2. Dr Gopi Vemuri, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT Data Monitoring Committee Members: 1. Dr Ahmed Elazabi, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT 2. Dr Kuldip Bakaya, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT

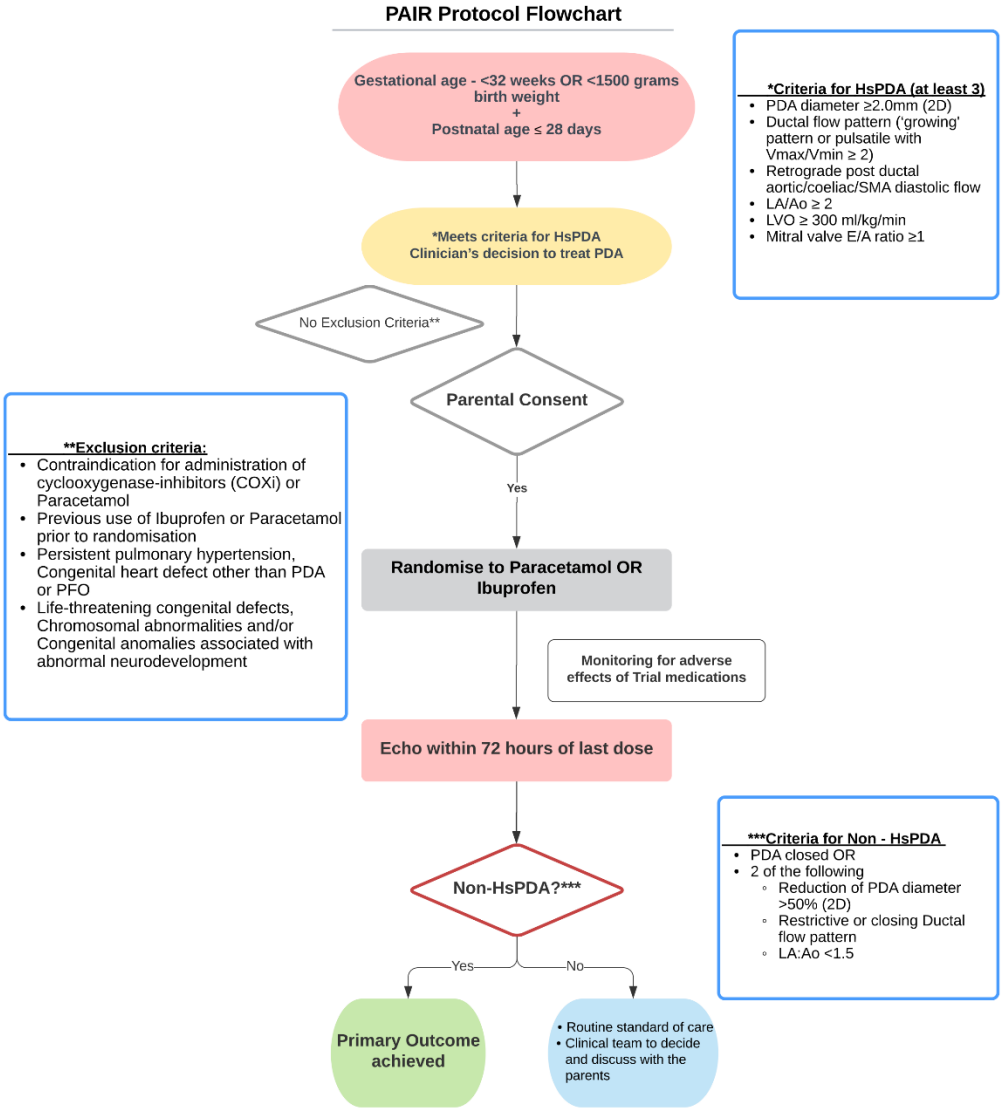
CONTENTS Page number

1. General Information

1.1 Trial Summary

Trial Title	PAIR (Paracetamol and Ibuprofen Research) Study: A randomised controlled trial comparing intravenous (IV) Paracetamol with IV Ibuprofen in the management of haemodynamically significant patent ductus arteriosus	
Short Title	The PAIR study	
Clinical Phase	Phase II/III	
Trial Design	Randomised controlled trial	
Trial Participants	Preterm infants (born at <32 weeks gestational age or birth weight < 1500 grams) with haemodynamically significant patent ductus arteriosus (hsPDA) who are ≤ 28 days old	
Planned Sample Size	32 babies	
Treatment duration	3 days	
Follow up duration	Till 36 weeks corrected postnatal age	
Planned Trial Period	Two years	
	Objectives	Outcome Measures
Primary	To study the efficacy of Paracetamol (proposed new treatment) in treating hsPDA in comparison to Ibuprofen (current standard treatment) in preterm infants	Conversion of hsPDA (defined in section 8.4) to non-hsPDA (defined in section 8.5)
Secondary	1. To compare BPD free survival at 36 weeks post menstrual age (PMA) 2.To compare the incidence of complications of prematurity in each group 3.To record any evidence of adverse effects with Paracetamol or Ibuprofen	1. BPD free survival at 36 weeks PMA 2. a) NEC (Bell stage ≥IIa) b) Significant IVH (grade 3/4) c) ROP requiring treatment 3. a) Renal impairment (elevated urea and creatinine > upper limit of normal range) b) Hepatic impairment (elevated liver enzymes ALT or AST > upper limit of normal) c) Significant gastrointestinal or non-gastrointestinal bleeding requiring intervention
Investigational Medicinal Product Dose, Route of Administration	Group A (Ibuprofen group) Intravenous Ibuprofen loading dose at 10mg/kg, followed by 5mg/kg IV once daily for two more doses each given at 24-hour intervals. Group B (Paracetamol group) Intravenous Paracetamol at a loading dose of 20mg/kg/dose followed by 10mg/kg/dose will be given four times daily for three days (total daily dose of 40-50mg/kg).	

1.2 Trial Flow Chart



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1.3 List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BPD.	Bronchopulmonary Dysplasia
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
hsPDA	Haemodynamically significant Patent Ductus Arteriosus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MHRA	Medicines and Healthcare products Regulatory Agency
NICU	Neonatal Intensive Care Unit
NEC	Necrotising Enterocolitis
PDA	Patent Ductus Arteriosus
PI	Principal Investigator
PMA	Post menstrual age
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

2. Roles and Responsibilities

a) Trial Steering Committee Members:

1. Dr Abhijeet Godhamgaonkar, Clinical lead, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT

2. Dr Gopi Venmuri, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT

b) Data Monitoring Committee Members:

1. Dr Ahmed Elazabi, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT

2. Dr Kuldip Bakaya, Consultant Neonatologist, Department of Neonatology, Wythenshawe Hospital, Southmoor Road, M23 9LT

3. Background

Patent Ductus Arteriosus (PDA) is present in 40-60 percent of preterm infants. While Ductus arteriosus is important for foetal circulation, it is undesirable postnatally and is expected to close spontaneously as part of normal postnatal adaptation in term infants. However, prolonged ductal patency is often seen as a complication of extreme preterm birth[1]. A persistent PDA with a large left to right ductal shunt may be 'haemodynamically significant' (hsPDA) resulting in pulmonary hyper-perfusion and systemic hypo-perfusion[2]. The association of a PDA with an increased incidence of pulmonary haemorrhage, bronchopulmonary dysplasia and prolonged need for ventilatory support is ascribed to pulmonary hyper-perfusion, whereas necrotising enterocolitis, renal failure, cerebral haemorrhage, and periventricular leukomalacia are consequences of systemic hypo-perfusion.

In the UK, Ibuprofen (a non-steroidal anti-inflammatory drug, NSAID) is used to treat hsPDA in preterm babies. Though it is preferred over other NSAIDs like Indomethacin in view of less potential to cause intraventricular haemorrhage (IVH) or nephrotoxicity[3], it is not without its own side effects[4]. Recently, Paracetamol has been suggested as a safe alternative medication to Ibuprofen particularly in situations where Ibuprofen fails to influence the PDA or is contraindicated. There is some evidence suggesting that while Paracetamol may confer comparable treatment efficacy similar to Ibuprofen for PDA closure[3,6], it has a lower risk of adverse events in comparison to NSAIDs like Ibuprofen[4,5,6,7] particularly in relation to renal toxicity and gastrointestinal bleeding[5,6].

While Ibuprofen has been primarily associated with adverse effects like nephrotoxicity, gastrointestinal bleeding and perforation, use of Paracetamol has been associated to adverse effects like hepatic toxicity with elevated liver enzymes and hyperbilirubinemia.

Paracetamol is a medication that is recommended as a first-line antipyretic and analgesic in infants and has an excellent safety profile and track record for such use in the infant population.

While Paracetamol is licensed for use by BNFc (British National Formulary for Children) as an antipyretic in preterm infants more than 28 weeks' gestation, it is not yet licensed for use in PDA treatment in preterm infants[12]. Recently it has been used in the management of PDA with promising results [5,8,9,10]. However, the current available body of evidence is considered to be of moderate to low quality and hence its effectiveness and safety profile is not fully established in this patient population[10].

We have conducted a national survey[15] across 63 neonatal intensive care units (NICUs) in the United Kingdom between February and April 2020. The response rate was 95% (60/63). The survey disclosed widespread use of paracetamol while identifying that the practice remains variable, in absence of robust evidence. Strikingly, 95% of the respondents felt the need for a randomised controlled trial (RCT) to guide their practice. In keeping with an overwhelming interest across NICUs in UK, we propose this pilot study to address the safety and efficacy of paracetamol against ibuprofen using vigorous research methodology. The results of this study will inform a larger multi-centre trial, which will improve the ability of clinicians to make better evidence based clinical decisions and establish uniform practice recommendations.

4. Study Objectives and Endpoints:

The primary objective is to study the efficacy of IV paracetamol in treating hsPDA in comparison to IV ibuprofen in preterm infants born at less than 32 weeks' gestation OR less than 1500 grams birth weight.
Following the completion of the third day of trial medication administration, the end point for the primary outcome will be achieved.

5. Study Design:

This is a single centre prospective randomised pilot study which will be conducted at St Mary's Hospital NICU in Manchester. It is a level 3 neonatal intensive care unit. We aim to enrol 32 eligible preterm babies for the trial. Recruitment duration will be 2 years. All infants who are symptomatic clinically and suspected of having PDA will have an echocardiogram to confirm presence and size of PDA. Decision to treat infants with hsPDA (defined in section 8.4) will lie with the Clinician. Once a decision is made to treat, parents would be approached, the study introduced, a parent information leaflet given and if they consent to enrol their baby (ies) in the trial. Once consented, infants will be randomly allocated to receive either IV Ibuprofen for 3 days or IV Paracetamol for 3 days. Following the completion of the treatment course, the echocardiogram will be repeated within 72 hours to re-assess the Ductus Arteriosus (DA). If the DA converts to non-hsPDA (defined in section 8.5), this will be regarded as the trial end point for primary outcome.

5.1 Selection of Study Participants Inclusion Criteria:

- Gestational age - <32 weeks OR birth weight < 1500 grams
- Postnatal age ≤ 28 days

- Meets criteria for hsPDA
- Clinician's decision to treat PDA

5.1.2 Exclusion Criteria:

- Contraindication for administration of Ibuprofen (cyclooxygenase-inhibitors) or Paracetamol, such as: active bleeding (e.g. intracranial or gastrointestinal haemorrhage), thrombocytopenia (<50x10^9/L), renal failure (raised creatinine (>100 micromole/l) or oliguria (<0.5 mL/kg/hour), known or suspected necrotising enterocolitis, any gastric or intestinal perforation, pre-treatment abnormal liver function tests (ALT > upper normal limit of the reference range, Bilirubin > NICE exchange phototherapy level[13]).
- Previous use of Ibuprofen or Paracetamol prior to randomisation.
- Persistent pulmonary hypertension (ductal right-to-left shunt ≧33% of cardiac cycle).
- Congenital heart defect, other than PDA or PFO.
- Life-threatening congenital birth defects.
- Chromosomal abnormalities and/or congenital anomalies associated with abnormal neurodevelopment.

5.2 Recruitment of Participants

5.2.1 Initial Contact

All infants admitted in our neonatal unit, who are symptomatic and clinically suspected of having PDA will have an echocardiogram to confirm presence, size and characteristics of the PDA. This is in keeping with current routine standard of care. Decision to treat infants with hsPDA will lie with the clinician. Once a decision is made to treat PDA, the clinical care team will discuss with the clinical research team to check whether the baby meets the eligibility criteria and to ensure that it is appropriate to approach parents to discuss the study. If baby meets eligibility criteria, the clinical research team will introduce the study to parents.

5.2.2 Recruitment

A Patient Information Sheet will be provided to the parents to provide information regarding the trial. Parents will be given sufficient time (ideally 24 hours) to read the leaflet and ask any questions. A written informed consent will be obtained from a person with parental responsibility prior to participation in the trial.

5.2.3 Randomisation Procedure

Computerised randomisation through sealedenvelope.com website will assign the neonate to medical treatment with either IV Ibuprofen or IV Paracetamol, both of which will be intended to close the PDA. There will be no allocation concealment during the trial. This trial will be single blinded and assessors (clinicians interpreting the echocardiogram) will also be blinded to the treatment arm.

5.2.4 Sample Size Calculation

This is a pilot study designed to assess whether it is possible to run a trial to assess the efficacy of using Paracetamol compared to Ibuprofen. The study will aim to recruit 32 patients which will allow estimation of the sample size and power calculation for the larger multicentre RCT[14]

5.2.5 Withdrawal from Study Treatment

The right of a participant to refuse participation after initial consent without giving reasons will be respected and parents will be assured that this decision will not impact on their baby's clinical care. In the event of parental desire to withdraw from the study, the participants will not be receiving any further intervention. However, the data will be included on any participant who has received the trial medications on intention to treat basis.

5.2.6 Exit criteria

Following observations will be considered as exit criteria:

a) Ibuprofen associated: active gastro-intestinal bleeding and/or perforation, evidence of renal dysfunction e.g. oliguria <0.1 ml/kg/hour and/or raised Creatinine >200 micromol/l; evidence of platelet dysfunction (may manifest with petechiae) with absolute platelet count < 25 x $10^{9.}$

b) Paracetamol associated: Signs/evidence of liver dysfunction i.e., raised liver transaminases ALT/AST > ten times above upper reference range, unexpected jaundice with bilirubin above NICE exchange transfusion threshold[13].

c) Significant gastrointestinal or non-gastrointestinal bleeding requiring resuscitation.

5.3 Treatment details

Ibuprofen:

- IV preparation 20 mg/2 ml solution for infusion ampoules
- Marketed and packaged by Recordati Rare Diseases UK Ltd
- Labelled as Ibuprofen (Pedea) and kept in IV drug cupboard in NICU
- Intravenous infusion administered over 15 minutes (section 5.3.1)
- Accountability: Section 7.12

Paracetamol:

- IV preparation 100mg/10 ml solution for infusion ampoules
- Marketing authorisation by several companies in UK and procured in keeping with local practice
- Labelled with active ingredient Paracetamol and kept in IV drug cupboard in NICU
- Intravenous infusion administered over 15 minutes (section 5.3.2)
- Accountability: Section 7.12

5.3.1 Group A (Ibuprofen group)

IV Ibuprofen loading dose at 10mg/kg, followed by 5mg/kg IV once daily for two more

doses each given at 24-hour intervals.

5.3.2 Group B (Paracetamol group)

IV Paracetamol at a loading dose of 20mg/kg/dose followed by 10mg/kg/dose will be given four times daily for three days[6,8] (total daily dose of 40-50mg/kg). There is some evidence in the literature that doses of up to 60mg/kg/day are tolerated safely in extreme preterm babies[6,8].

5.3.3 Concomitant medication

Paracetamol: Use of blood thinners like Warfarin or Heparin should be cautiously administered in conjunction with Ibuprofen because of theoretical possibility of bleeding. Any infants on enzyme-inducing antiepileptic drugs like Phenobarbitone, Rifampicin or Phenytoin will be monitored closely with caution due to its potential interaction with Paracetamol.

Ibuprofen: Steroid use is not recommended in conjunction with Ibuprofen and any such use in special situations will be very closely monitored owing to its potential to cause gastro-intestinal haemorrhage. Ibuprofen may decrease the clearance of aminoglycosides such as gentamicin and strict surveillance of antibiotic levels will be done during coadministration with ibuprofen. Ibuprofen may also reduce the effect of diuretics, so should be used cautiously.

6. Study methodology

Following informed consent in eligible babies (diagnosis of hsPDA confirmed with baseline echocardiogram) and electronic randomisation, allocation of babies in Paracetamol group (group A) and Ibuprofen group (group B) will be done. A 3-day treatment will be initiated with the trial medications.

6.1 Standard monitoring during administration of Trial medications

All infants on trial medications will be monitored as part of standard care. Their vital parameters would be recorded and analysed as per the unit policy. Blood tests like full blood count (FBC), neonatal profile and liver function tests (liver enzymes and Bilirubin) would be performed as per the unit policy. No additional blood test samples will be required.
IV Paracetamol may be associated with raised liver enzymes and hyperbilirubinemia. IV Ibuprofen may be associated with renal impairment, bleeding and gastro-intestinal complications. The clinical team will be alert for any side effects being displayed in infants participating in either arm during the trial.

6.2 Additional investigations and care following completion of Trial medications

An echocardiogram will be performed by designated neonatologists (on the delegation log) within 72 hours after the last dose of trial medications on day 3, to assess the Ductus Arteriosus (DA). Echocardiograms will be reported by the Paediatric cardiologists in keeping with the routine standard of care.
Following completion of the trial medications, if hsPDA persists, participating infants will return to routine standard of care and clinicians will be able to decide on further management of the PDA in keeping with the unit policy.

7. Safety Reporting: Definitions

7.1. 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.

7.1.1. 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.

7.1.2 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:

- Anaemia requiring transfusion
- Clinically significant intracranial abnormality on cranial ultrasound scan – intracranial haemorrhage or white matter injury
- Coagulopathy requiring treatment
- Culture proven sepsis
- Death (unless unforeseeable in this population)
- Fluid retention
- Gastrointestinal bleeding
- Haematuria

- Haemothorax
- High blood creatinine level (defined as >100 µmol/L)
- Hyperbilirubinemia necessitating exchange transfusion
- Hyperglycaemia
- Hypoglycaemia
- Hypotension treated with inotropes
- Impaired renal function (urine output 100 µmol/L)
- Raised liver enzymes (ALT>100)
- Raised serum bilirubin (Serum bilirubin above the exchange line)
- Low serum sodium level/hyponatremia (defined as sodium <130 mmol/L)
- Necrotising enterocolitis
- Neutropenia (defined as <1.0 mmol/L)
- Pneumothorax requiring treatment
- Pulmonary hypertension requiring treatment with pulmonary vasodilator
- Respiratory failure
- Seizures requiring treatment
- Significant pulmonary haemorrhage
- Spontaneous intestinal perforation
- Thrombocytopenia (Platelet count <150 $x10^9$/L)

7.1.3 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 7.2.

7.2 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.

7.2.1 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.

7.2.2 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 Sodium Chloride of ibuprofen and paracetamol is contained within section 4.8 of the SmPCs.

7.3 Serious adverse events (SAE) and Serious adverse reaction (SAR) reporting

All SARs and SAEs whether related or unrelated will be reported within 24 hours of the site becoming aware of the event. The SAE form will describe the nature of event, date of onset, severity, corrective therapies given, outcome and causality (and expectedness, for related events). The CI would sign the SAE form. If the CI is not available, then another clinician (PI) listed on the delegation log will sign the form. Should all delegated signatories be absent, the report would be sent unsigned, in order to meet the 24-hour requirement.

The report will then be sent by email to the sponsor's adverse event reporting email address: adverse.events@mft.nhs.uk. Additional information would be sent within five days if the event has not resolved at the time of reporting.

7.4 Assessment of causality

The Investigator responsible for the care of the participant will assess whether the AE/SAE is likely to be related to treatment according to the definitions mentioned above. All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, almost certainly) to the study treatment will be considered as reactions and will be assessed for expectedness. If concomitant or rescue/escape drugs are given, the Investigator will also make an assessment of whether the AE/SAE is likely to be related to an interaction between the study treatment and concomitant or rescue/escape drugs or whether the AE/SAE might be linked to either the study treatment or concomitant or rescue/escape drugs but cannot be attributed to only one of these drugs. All AEs/SAEs judged as being related (e.g. possibly, probably, almost certainly) to an interaction between the study treatment and concomitant or rescue/escape drugs, or any AE/SAE with unknown cause would be considered to be ARs/SARs.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment would be considered and investigated.

7.5 Assessment of expectedness

The sponsor's assessment of expectedness for events considered to be possibly, probably or almost certainly related to the IMP will be made by the CI (or designated person like PI, in the CI's absence) following the receipt of the SAE form. If the CI is the reporting investigator the assessment of expectedness will be undertaken by the designated individual who is assigned the duty in CI's absence.

Events considered unrelated to the IMP do not need to be assessed for expectedness.

7.6 Follow up procedures

After initially recording an AE or recording and reporting an SAE, the Investigators would follow each participant until resolution. All information and follow up information on SAEs, SARs and SUSARs would be reported to the Sponsor in real time and sent to adverse.events@mft.nhs.uk to ensure the reports are monitored appropriately.

7.7 Criteria for premature termination of study

The study may be considered for termination if

- There is new safety data or evidence from other studies;
- There is concerns from safety data (number and nature of SUSARs);
- If fewer than three babies were recruited over the first six months.

The decision to terminate the study would be taken by TSC.

7.8 Regulatory reporting requirements

Fatal or life threatening SUSARs will be reported by the Sponsor no later than seven calendar days after the Sponsor first became aware of the reaction. All other SUSARs will be reported no later than 15 calendar days after the Sponsor is first aware of the reaction.

7.9 Safety reports / Development Safety Update Report (DSUR)

The Development Safety Update Report (DSUR) will be prepared and submitted by the Sponsor in conjunction with the Chief Investigator. This will be submitted annually within 60 days of the Data Lock Point (DLP). The DLP will be set at the last day of the one-year reporting period.

7.10 Potential serious breach

Following the decision that a serious breach of the protocol or GCP has occurred, the TMG will liaise with the Sponsor and other involved parties to establish:

i. The extent of the breach
ii. Whether a substantial amendment or urgent safety measures is required
iii. Other corrective actions/training that are identified

If the Sponsor has clear and unequivocal evidence that a serious breach has occurred, the sponsor would notify the MHRA within seven days, and investigate and take action simultaneously or after notification.

The Sponsor will inform the TMG of its decision regarding the potential serious breach and confirm that onward reporting to the REC and the MHRA has occurred where appropriate. Any requests for additional information from the Sponsor or MHRA will be actioned promptly and open communication will be maintained with Sponsor and oversight committees to ensure appropriate corrective actions are taken and documented.

7.11 Urgent safety measures

An urgent safety measure is a procedure not defined by the protocol. Implementation may take place prior to authorisation by the regulatory authority and REC in order to protect clinical study participants from any immediate hazard to their health and safety.

If an immediate hazard to the health and safety of participants in PAIR is detected, the sponsor shall immediately, and in any event no later than three days from the date the measures are taken, give written notice to the regulatory authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

The CI and sponsor will together determine the appropriate course of action. Once the appropriate course of action has been determined, the CI must take the agreed action to ensure trial subjects are made safe.

The MHRA and REC will be informed of Urgent Safety Measures by means of a completed substantial amendment form.

If PAIR study is temporarily halted for any reason, the sponsor would notify the MHRA and Ethics Committees immediately and at least within 15 days from when the trial is temporarily halted. The notification would be made as a substantial amendment using the Notification of Amendment form and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt.

In this case the study may not recommence until authorised to do so by the responsible regulatory authority and REC.

If the study is temporarily halted and the decision is then made to permanently end the trial before the date specified for its conclusion (in the application), the Sponsor would notify the regulatory authority and REC within 15 days of the date of the decision to terminate the trial by submitting a declaration of End of Trial form and including a description of the reason for discontinuation.

7.12 Accountability

Medications are kept in the neonatal unit as standard stock. If there is any stock supply disruption, available stock will be checked before randomising a subject. Standard prescribing practice will be followed.
As per risk-adapted approach to IMP accountability there is no requirement for:

i) Shipping receipt and destruction records
ii) Master or patient level accountability logs
iii) Recording batch numbers and expiry dates

As the subjects will be inpatients, compliance will be recorded on the medication chart as per standard practice.

8 Outcomes

8.1 Primary Outcome

Conversion of hsPDA (defined in section 8.4) to non-hsPDA (defined in section 8.5)

8.2 Secondary Outcomes and Follow-up duration

i) BPD free survival at 36 weeks PMA
ii) Incidence of complications of extreme prematurity

- NEC (Bell stage ≥IIa)
- Significant IVH (grade 3/4)
- ROP requiring treatment

iii) Evidence of adverse effects of Ibuprofen/Paracetamol

- Renal impairment (elevated urea and creatinine > upper limit of normal range)
- Hepatic impairment (elevated liver enzymes ALT or AST > upper limit of normal)
- Significant gastrointestinal/ non-gastrointestinal bleeding requiring intervention

Follow-up Duration: Participating infants will undergo follow-up till the point of discharge to home or a corrected gestational age of 36 completed weeks, whichever comes earlier.

As this is a Pilot Trial, we will also look at the feasibility of the Trial design, including recruitment, retention, acceptability of randomisation, primary and secondary outcomes along with data on any adverse effects of the trial medications. The results of these outcomes will inform the feasibility and help with sample size calculation for an envisaged larger multicentre randomized controlled trial.

8.3 Other recorded study parameters

The following clinical details/findings will be documented using standard medical records; Administration of antenatal steroids • Maternal disease (pre-eclampsia) • Mode of delivery • Multiple birth • Duration of rupture of membranes prior to birth • Gestational age at birth • Birth weight • Apgar scores at 5 minutes • Blood gas analysis • Resuscitation after birth • Surfactant administration • Postnatal steroid administration. These factors are taken into consideration as part of routine standard of care for treating PDA.

Echocardiogram evidence of changes in cardiovascular haemodynamics, ductal size changes and any evidence of changes in ductal steal pre- and post-treatment with trial medications.

None of the study parameters would need review of maternal medical records.

8.4 Definition of Hemodynamically significant PDA (hsPDA)

The following echocardiographic indices and thresholds should be used to define as hsPDA[11]

i) PDA diameter ≥2.0 mm in 2D
ii) Ductal flow pattern (‘growing' pattern or pulsatile with Vmax/Vmin ≥ 2)
iii) Retrograde post ductal aortic/coeliac/SMA diastolic flow
iv) LA/Ao ratio ≥ 2
v) LVO ≥ 300 ml/kg/min
vi) Mitral valve E/A ratio ≥ 1

The diagnosis of hsPDA will be made in the presence of supportive clinical signs and at least three of the above echo indices.

8.5 Definition of non-hsPDA following treatment

An echocardiogram will be carried out within 72 hours of the last dose and PDA will be classified as non-hsPDA based on the following criteria –
PDA closed OR any two of the following three parameters

i) Reduction of PDA diameter >50% (2D)
ii) Restrictive or closing Ductal flow pattern
iii) LA: Ao ratio < 1.5

9 Study Monitoring

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A detailed risk assessment is performed for each trial to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial; this is outlined in the Trial Monitoring Plan. Monitoring activities will be carried out by the Sponsor / Sponsor representative.

The monitoring of the PAIR study will be in line with the Sponsor organisation policies.

9.1 Data Collection

Data will be collected from participants at indicated time points into source documents.

All SAEs will be reported by completing the information on the SAE report form and sent to the Sponsor. A Data Management Plan will be in line with the Sponsor and host organisation policies.

9.2 Direct access to data

The Chief Investigator will permit study-related monitoring, audits, REC review, and regulatory inspection and provide direct access to source data and documents.

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). A source document identification list will be produced prior to trial initiation.

9.3 Site monitoring

The investigators will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents to sponsors for monitoring purposes.

10 Confidentiality and data protection

10.1 Confidentiality

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, Regulatory Authorities, or the REC.

The Investigator and study site staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

Prior written agreement from the Sponsor or its designee would be obtained for the disclosure of any confidential information to other parties.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. Participants will be identified using only their unique study number, date of birth, and initials on the database.

10.2 Data protection

Data will be collected in accordance with the "Caldicott Principles", the Data Protection Act (DPA) and the General Data Protection Regulation (GDPR). All babies recruited will be allocated a screening number and randomisation number which will be linked to their identifiable information held in a separate file stored within the research unit.

All outcome data will be entered onto a password protected database within the NICU research office, accessible only to members of the research team. All electronic data will be anonymised, and no identifiable data will be stored on this database.

Published results will not contain any personal data that could allow identification of individual participants.

11 Study conduct

Protocol violations / deviations / serious breaches
In the event of a breach of protocol or GCP the trial team would follow the instructions found in section 7.11 of this document and report appropriately.

12 Study record retention

In line with the Medicines for Human Use (Clinical Studies) Regulations, once data collection is complete on all participants, all data will be stored for 25 years. Long-term off-site data archiving facilities will be advised for storage.

13 End of study

The end of the study is defined to be the date of database lock. This is the date on which data modification privileges are withdrawn from the study database.

The Sponsor and/or the TSC will have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC/MHRA within the required timeframe (15 days if the study is terminated prematurely or 90 days otherwise). Investigators will inform participants of any premature termination of the study and ensure that the appropriate follow up is arranged for all involved. A summary report of the study will be provided to the REC within the required timeframe.

14 Peer review

This proposal has been peer reviewed by

i) Dr C Harikumar, Head of neonatal services & Lead consultant neonatologist, University hospital of North Tees, Stockton on Tees, TS19 8PE, United Kingdom.

ii) Prof APS Hungin, Faculty of Medical Sciences, Newcastle University, 4 Butts Lane, Egglescliffe, Stockton on Tees, TS16 9BT, United Kingdom.

15 Indemnity

The PAIR study is sponsored by the Manchester University NHS Foundation Trust. The Manchester University NHS Foundation Trust cover for negligent harm is in place through the Clinical Negligence Scheme for Trusts. For NHS Sponsored research HSG(96)48 reference no.2 refers 'If there is any negligent harm during the study when the NHS body owes a duty of care to their person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim'.

16 Statistical Analysis

All analyses will be conducted on an intention-to-treat basis and will include all patients who have undergone randomisation. Both intention-to-treat and per-protocol analysis will be done to assess the effect of contamination and quantify the protocol violations on the primary outcome.

All variables will be examined descriptively with appropriate statistics and graphics for completeness and form. No imputation will be done for missing data, but numbers will be noted and used to inform the larger study.

The primary outcome will be presented as a frequency with 95% binomial confidence intervals. Exploratory comparisons between groups will be made using a fisher's exact test. Exploratory univariate logistic-regression analysis will be used to identify potential baseline covariates associated with the primary outcome.

Secondary outcomes will be presented descriptively using appropriate statistics both overall and by group. Exploratory discrete comparisons will be made via Fisher's exact test. Continuous

variables will be compared with an unpaired t-test or the Mann–Whitney U (Wilcoxon rank sum) test. For time dependant variables, survival statistics will be presented.

As this is a pilot trial, adverse events for both groups will be described both as total number of events and number of patients experiencing each event, with consideration for those occurring due to the proposed treatment (Paracetamol/Ibuprofen) for which we will use descriptive statistical analysis. All analyses would be conducted with the use of SPSS software (IBM) and R v3.6.0. A two-sided p-value of less than 0.05 will be considered to indicate statistical significance. The statistical analysis will be supervised by Dr Catherine Fullwood, Senior Statistician, Manchester University NHS Foundation Trust.

17 Ethics and dissemination

The trial will follow international code of ethics for clinical trials. The trial protocol will be approved by a Research Ethics Committee. All serious adverse events will be recorded in accordance with the protocol and analysed accordingly. The trial will also be registered on clinical trials.gov.

18 Publication Plan

At the end of the study, it is intended that the results will be analysed and published in medical journals and will be presented in medical seminars and conferences. None of the individual participants will be identified in any report or the publication of the study. A copy of the journal article can be requested from the Chief investigator.

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