**Title: Management of Patent Ductus Arteriosus (PDA) in babies admitted to UK neonatal units: a population-based study using the National Neonatal Research Database**

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**Sponsor**

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the

study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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# 1 INTRODUCTION

## 1.1 Background

The ductus arteriosus is a short blood vessel connecting the two main arteries in fetal life and usually closes in the first few days after birth. This closure is delayed in over half of preterm babies, resulting in a patent (open) ductus arteriosus (PDA). This leads to extra blood flowing to the lungs and less blood flowing to other organs, which can cause problems and lead to extra load on the heart. Such PDAs are termed ‘haemodynamically significant’. Adverse outcomes such as death, bronchopulmonary dysplasia (BPD) and necrotising enterocolitis (NEC) have been associated with haemodynamically significant PDAs, although a causal link has not been established (1).

Management options include conservative management, medical therapy with cyclooxygenase (COX) inhibitors (ibuprofen, indomethacin, paracetamol), and surgery. Both medical and surgical options have potential adverse effects (2). Despite numerous observational and randomised controlled studies, there is no consensus on the management of PDA (3). It is unclear whether intervention is beneficial as spontaneous closure is common in the first seven days of life (4), and there is little evidence that PDA closure changes clinical outcomes in preterm babies like BPD and NEC (5, 6). Importantly, even when closure of PDA is desired, the optimal timing, choice of medical therapy, and indication for surgery are debated. Wide variation in PDA management is anecdotally reported in the United Kingdom, but has not been systematically described.

This project will use the National Neonatal Research Database (NNRD) which holds detailed population-level data since 2007 for all babies admitted for neonatal care in England, Wales and Scotland. The NNRD holds data records on over 1 million babies, and over 10 million daily care days.

## 2 STUDY OBJECTIVES

The aim is to describe the management of patent ductus arteriosus in preterm babies admitted to neonatal units in England and Wales over a 10 year period (2010-2019).

1. To quantify the number and proportion of preterm babies, born <32 weeks gestation, who receive medical and/or surgical intervention for PDA.
2. To describe the infant background and clinical characteristics at the time of medical or surgical PDA intervention and compare them to babies within similar gestational age (GA) groups who did not have an intervention.
3. To determine the postnatal age of medical or surgical PDA intervention.
4. To describe the outcomes of babies treated for PDA (including BPD, NEC, mortality, ventilatory days, brain injury, retinopathy of prematurity) and compare with babies of similar gestational age and neonatal unit with babies those that did not receive PDA intervention
5. To explore the presence of temporal trends and geographical variation in PDA management for the aims 1-4.

## 3 STUDY DESIGN

This is a descriptive retrospective cohort study. This is a retrospective cohort study using anonymised, routinely recorded clinical data held in the NNRD. The NNRD holds data from all babies admitted to National Health Service (NHS) neonatal units in England, Scotland and Wales (approximately 80,000 babies annually; 8,000 less than 32 weeks gestation ); all NHS neonatal units in England and Wales have been contributing data to the NNRD since 2012, all NHS neonatal units in Scotland have been contributing to the NNRD since 2015. Contributing neonatal units are known as the UK Neonatal Collaborative (UKNC). Data are extracted from point-of-care neonatal electronic health records completed by health professionals during routine clinical care. A defined data extract, the Neonatal Dataset of approximately 450 data items (7), is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster NHS Foundation Trust where patient episodes across different hospitals are linked and data are cleaned (queries about

discrepancies and implausible data configurations are fed back to health professionals and rectified) (8). Data items include demographic and admission items (e.g. maternal conditions, gestation, birth weight), daily items (e.g. respiratory support, medication, surgery, feeding information), discharge items (e.g. feeding and weight at discharge) and ad hoc items (entered if and when they occur, e.g. suspected infection, ultrasound scan findings, abdominal x-ray findings.

### 3.1 STUDY OUTCOME MEASURES

The primary outcome is the proportion of babies that received a medical or surgical intervention for PDA closure

The following secondary outcomes were analysed for those that received an intervention:

- Time to come off invasive respiratory support (postnatal age)

- Timing of medication or surgery (postnatal age in days)

- Duration of medication (number of days)

- Clinical condition at the time of intervention for PDA including respiratory support, cardiovascular support, feeding

-Time to come off oxygen (postnatal age)

- Brain injury (intraventricular haemorrhage grade 3/4 or cystic periventricular leukomalacia or stroke or meningitis or hypoxic ischaemic encephalopathy)

- Necrotising Enterocolitis: 2 definitions i) severe NEC (confirmed at surgery or death) ii) NNAP/Vermont Oxford definition

-Spontaneous intestinal perforation

- Retinopathy of Prematurity requiring treatment

- Survival to discharge from neonatal care

- Pulmonary Haemorrhage

- Chronic Lung Disease at 36 weeks corrected age (National Neonatal Audit Programme (NNAP) definition))

- Receiving breast milk at discharge

- Intensive care days

- Invasive ventilation days

- Parenteral nutrition days

## 4 PARTICIPANT ENTRY

There is no patient recruitment; this is a database retrospective analysis.

### 4.1 INCLUSION CRITERIA

Eligible babies within the NNRD include those who:

1. Were born and admitted to a neonatal unit between 1st Jan 2010 and 31st December 2019

2. Born and received care in neonatal units in England and Wales (part of UKNC and therefore contributing data to the NNRD)
3. Have a recorded gestational age at birth <32 weeks

### 4.2 EXCLUSION CRITERIA

Babies with missing data for principal background variables will be excluded. These are gestational age at birth, sex and place of birth.

We will exclude units from Scotland which only started contributing data from 2015.

## 5 STATISTICS AND DATA ANALYSIS

### 5.1 Analysis plan

We will describe the background characteristics of babies born less than 32 weeks in England and Wales who do and do not receive intervention for PDA. Analyses will be conducted in three gestational age categories (<27 weeks, 27 to 29 weeks, 30 to 31 weeks). Comparisons will be made within networks and gestational age groups who do and do not receive medical and/or surgical intervention for PDA closure. Results will be presented using medians (interquartile ranges) and proportions for continuous and categorical variables, respectively. Chi-squared test will be used to compare categorical data. For continuous variables, the t-test is applied with normally distributed data, and the Wilcoxon test otherwise.

### 5.2 Potential missing data

For surgical intervention, babies who are not already cared for in a cardiac surgical centre, will require transfer to one of the following units: Alder Hey Children's Hospital, Birmingham Children's Hospital, Royal Manchester Children's Hospital, Freeman Hospital Newcastle, Leeds General Infirmary, Leicester Hospital, Bristol Royal Hospital for Children, Great Ormond Street Hospital for Children (London). Royal Brompton Hospital (London), Evelina Children's Hospital (London), Southampton General Hospital. Some of these centres are Paediatric Intensive Care units which do not contribute data to the NNRD. We will account for the potential missing daily data for babies transferred to non-neonatal centres.

### 5.3 Sample size

The denominator is estimated to be around 70,000 over 10 years as approximately 7,000 babies are born less than 32 weeks each year in England and Wales.

## 6 REGULATORY ISSUES

### 6.1 ETHICS APPROVAL

No patient identifiable information will be used in this study and only existing anonymised data held in the NNRD will be used. The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee approval, 16/LO/1093, and Confidential Advisory Group (CAG) approval, ECC 8-05(f/2010), to form the NNRD.

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human

### 6.2 CONSENT

Not applicable

### 6.3 SPONSOR AND INDEMNITY

The sponsor is Imperial College London; insurance policies are held that apply to this study.

### 6.4 FUNDING

This is part of an Imperial College Masters in Public Health project and receives no additional funding

### 6.5 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

## 7 STUDY MANAGEMENT

This project will be based at the Neonatal Data Analysis unit, Chelsea and Westminster Hospital, Imperial College Campus. The NDAU manages and hosts the National Neonatal Research Database. All necessary governance structures are in place. The UK Neonatal Collaborative (all units in the UK) submit data with Caldicott Guardian approvals.

The database to be used in this study is the NNRD; researchers, clinicians, managers, commissioners, and others are welcome and encouraged to utilise the NNRD. More details are available here: http://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

## 8 PUBLICATION POLICY

The results will be published in an academic journal and presented at conferences. The UK Neonatal Collaborative will be named collaborators and will be acknowledged in all academic publications.

## 9 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

## 10 REFERENCES


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## 11 Appendix 1. Data extraction

| **Purpose** | **NNRD data items to extract** |
|---|---|
| Patient characteristics | Birthweight, sex, gestational age, ethnicity |
| Maternal factors | Prolonged rupture of membranes >24 hours<br>Antenatal steroids antenatally |

| | |
|---|---|
| To identify babies who received medical intervention for PDA closure<br><br>To describe postnatal age of medical intervention | *Daily data: cardiovascular and medications*<br>Any baby who received<br>i) ibuprofen OR<br>ii) indomethacin OR<br>iii) paracetamol AND without surgery the preceding 2 days |
| Identifying babies who received surgical interventions for PDA closure<br><br>To describe postnatal age of surgical intervention | *Daily data: cardiovascular*<br>Daily data indication PDA surgical intervention AND infant cared for in a cardiac centre |
| Neonatal unit information to determine if cardiac surgical centre and for comparisons | *Episodic admission and discharge information:* regarding neonatal unit, whether transferred, name of unit transferred to, reason for transfer *e.g. ongoing cardiac specialist* |
| To describe the clinical condition of baby at the time of intervention and post intervention | *Daily data: respiratory support (mode of ventilation), cardiovascular (inotropic support), feeding (enteral and parenteral nutrition)* |
| Outcomes | *Diagnoses and daily data*<br>Brain injury (intraventricular haemorrhage grade 3/4 or cystic periventricular leukomalacia or stroke or meningitis or hypoxic ischaemic encephalopathy)<br>Necrotising enterocolitis (all diagnoses “confirmed NEC”)<br>Necrotising enterocolitis (NNAP related items including clinical and radiological signs at the time of diagnosis and management)<br>Spontaneous intestinal perforation<br>Retinopathy of Prematurity requiring treatment<br>Survival to discharge from neonatal care<br>Pulmonary Haemorrhage<br>Chronic Lung Disease at 36 weeks corrected age (NNAP definition)<br>Receiving breast milk at discharge<br>Intensive care days |

| | |
|---|---|
| | Invasive ventilation days<br>Parenteral nutrition days |

KEYWORDS:
Patent ductus arteriosus
Prematurity
UK Neonatal Collaborative
Ibuprofen