Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

Understanding the healthcare burden of illness in moderate-, late-preterm and term neonates: pilot stages

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STUDY COORDINATION CENTRE: Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster Hospital campus
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Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator: Dr James Webbe

Co-investigators: Prof Elaine Boyle, Prof Samantha Johnson, Dr Cheryl Battersby, Prof Neena Modi, Prof Chris Gale

Statistician: Dr Mohammad Chehrazi

Data analyst: Kayleigh Ougham

Former-patient representatives: Karen Eaves-Lai, Nikki Stefanovic

Parent representatives: Angela Richard-Löndt, Laura Watson

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 1862**
Imperial College - Research Governance and Integrity Team (RGIT) Website

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Access to the NNRD through funds awarded to Prof Gale as part of an MRC Clinician Scientist grant. Data analysis funded as part of an NIHR Clinical Lecturer grant awarded to Dr Webbe. Stakeholder engagement work funded by a charitable grant from CW+ awarded to Dr Webbe.

This protocol describes the 'Understanding the healthcare burden of illness in moderate-, late-preterm and term neonates: pilot stages' 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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GLOSSARY OF ABBREVIATIONS

MRC	Medical Research Council
NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database

KEYWORDS
preterm, neonate, core outcomes set, NNRD, neonatal care

STUDY SUMMARY

TITLE Understanding the healthcare burden of illness in moderate-, late-preterm and term neonates: pilot stages

DESIGN Two pilot stages of overarching data linkage work, consisting of an epidemiological study and stakeholder engagement project

AIMS This is pilot work which will allow the creation of a data resource that can be used to assess the population healthcare burden of neonatal illness affecting moderate-preterm, late-preterm, and term neonates.

Epidemiological study

A) To describe the population of neonates born after 32^{+0} weeks+^{days} admitted to neonatal care in England and Wales.
B) To map neonatal admissions in this population by patient factors (such as gestational age and ethnicity) and organisational factors (such as geographic region of birth and level of neonatal unit of admission)
C) To identify patient and care factors associated with unwarranted variation in patterns of neonatal admission.
D) To describe core outcomes in moderate-, late preterm and term neonates admitted to neonatal care in England and Wales.

Stakeholder engagement project

A) To understand former patient, parent, and societal perspectives on linkage between existing data to evaluate the real-world impact of moderate-, late-preterm and term neonatal illness.

To obtain the qualitative data required for subsequent regulatory approvals for the overarching project (including Confidentiality Advisory Group approval)

METHODS: EPIDEMIOLOGICAL STUDY Epidemiological descriptive study. The background characteristics of admitted neonates will be described (including maternal, neonatal, and organisational factors) as will neonatal core outcomes.

Data source: De-identified data held in the National Neonatal Research Database (NNRD) will be used.

Background characteristics: Demographic data (e.g. sex, gestational age, year of birth), maternal factors (e.g. maternal age, pregnancy complications, receipt of antenatal steroids), neonate factors (e.g. Apgar score, admission temperature), and organisational factors (e.g. level of neonatal unit, neonatal network)

Outcomes: Survival

Short-term core outcomes: Sepsis, necrotising enterocolitis, brain injury on imaging, retinopathy of prematurity, adverse events, chronic lung disease/bronchopulmonary dysplasia

Long-term core outcomes: general gross motor ability, general cognitive ability, visual impairment or blindness, hearing impairment or deafness

Population: All neonates born after 32^{+0} weeks+^{days} postmenstrual age in England and Wales and admitted to a NHS neonatal unit over the period 1st January 2015 to 31st December 2022

Comparators: No comparator group; descriptive study

METHODS: STAKEHOLDER ENGAGEMENT PROJECT

Three stage mixed-methods approach including focus groups, an online survey, and in-depth interviews.

First four focus groups will be completed to discuss the project, the need for data linkage to improve neonatal outcomes, and to co-create an online survey. In stage two participants will complete the co-created online survey exploring family perspectives to retrospective linkage of neonatal, child-health and education databases. Finally, ten in-depth interviews will be held with survey participants who express negative views on the proposed linkage work to better understand potential barriers.

Participants:

Focus groups of six participants will include former neonates born after 32^{+0} weeks+^{days}, parents of this group, and representatives of wider society. A purposive sample will include both admitted and non-admitted families, fathers, and minority groups.

Online survey will be open to former patients, parents, healthcare workers, researchers, and wider society.

In-depth interviews will be held with ten survey participants who have expressed concern about the proposed linkage work. A purposive sample will include representation from former neonates, both admitted and non-admitted families, fathers, and minority groups.

Analysis plan:

Focus group responses will inform the co-created survey. Focus group, survey and interview responses will be used in a mixed-methods, inductive thematic analysis.

TITLE Understanding the healthcare burden of illness in moderate-, late-preterm and term neonates: pilot stages

DESIGN Two pilot stages of overarching data linkage work, consisting of an epidemiological study and stakeholder engagement project

1. PLAIN ENGLISH SUMMARY

BACKGROUND

Each year in the UK around 650,000 babies are born after 32 weeks of pregnancy. Around 90,000 are admitted to NHS neonatal units while the rest will receive any medical care needed in birth centres, on labour or postnatal wards. It has been shown that many neonatal unit admissions are not necessary, and that with appropriate support these babies could be cared for with their mothers. We also know that the care given to both admitted and non-admitted babies is very varied with many babies not getting the best possible care. This is because there has not been enough research to clearly tell healthcare professionals how these babies should be looked after. This can mean that similar babies get different care inappropriately, perhaps because they are born in different parts of the country or because of issues such as the ethnicity of the baby.

This is particularly worrying for three reasons. Firstly, this is an exceptionally large and important group of babies, they include over 98% of all livebirths and around 90% of all the babies admitted to neonatal care. Secondly, we know that for some babies the impact of any sickness in this early period may affect them throughout their whole lives, even leaving them more prone to serious problems, such as heart attacks, as adults. Finally, we know that babies who are born to families from ethnic minorities or deprived populations are more likely to be unwell after birth: this inequality should be reduced. Unfortunately, most neonatal research does not include any of these babies which is hampering efforts to improve the care that they receive.

Tackling this problem is challenging; in the past the costs and practical difficulties with following-up many babies over many years has meant that the ideal care for this group has not been identified. However, by linking data that is already routinely collected for all babies we plan to fully map the care that these babies are given after birth, identify how it affects long-term outcomes and identify how this care could be improved. This approach has been successfully used in other groups of babies. The overarching research project (called neoOUTCOMES) will be conducted in the future, but we are currently planning two crucial pieces of preparatory work: a descriptive study to map the care given and outcomes for babies born after 32 weeks who are admitted to a neonatal unit, and an engagement project to explore the views of former patients, families and wider society to the proposed data linkage work.

This work is the first, essential step in an exciting program of research that could improve the care given to a huge number of vulnerable babies each year, allowing them to grow up and thrive in their future lives.

AIMS

The main aim of this work is to gather the information needed to inform future research that will link existing databases to improve care and outcomes for babies born after 32 weeks of pregnancy.

For the two projects the specific objectives are as follows:
In the descriptive study we will describe which babies born after 32 weeks of pregnancy are admitted to neonatal units in England and Wales. We will also look at how rates of neonatal unit admission are affected by factors related to the babies (such as their gestational age at birth or ethnicity) and to the organisation of healthcare provision (such as which hospital they are born in) and explore whether some of the variability in neonatal admissions are not related to the baby who is admitted: this will tell us whether different babies are getting different (and possibly inappropriate) care. Finally, we will describe neonatal core outcomes in babies born after 32 weeks of pregnancy who are admitted to a neonatal unit.

In the engagement project we will describe the viewpoints of former patients, parents, and wider society on linkage between existing data to evaluate the impact of healthcare provided to neonates born after 32 weeks. We will also identify any specific concerns former patients, parents, and wider society have with the proposed linkage work and discuss possible solutions.

IMPORTANCE
This work is the first stage in the neoOUTCOMES research project that will identify the best way to manage the large group of babies born after 32 weeks of pregnancy.

Furthermore, the results of the descriptive study will describe which babies, born after 32 weeks of pregnancy, are admitted to neonatal units across the whole of England and Wales. It will also describe why they are admitted, currently this is not known. This project will improve understanding of why babies in these groups are admitted and identify cases where similar babies get different treatment: understanding this will help to ensure babies are treated equally and allow us to focus efforts to ensure that these babies all get the best possible care. This will include exploring whether factors like ethnicity or poverty influence the care babies get, which is of the utmost importance as we know that these babies face many disadvantages. Finally, this work will also tell us what the results of this care are by looking at the most important outcomes across the whole population.

The results of the engagement work will show whether former patients, parents and wider society feel that data linkage is acceptable for the proposed research and explore the acceptability of linkage without consent in this population. Understanding this is an essential step to allow the future neoOUTCOMES work to be planned and conducted in a manner sensitive to the concerns of those involved. The results of this engagement work will form the basis for a Confidentiality Advisory Group (CAG) application for linkage of routine data sources.

METHODS

The first study will map how babies born after 32 weeks are treated on neonatal units, and what outcomes they then experience. This will use routinely collected data from babies born between 2015 and 2022. Data is collected routinely for all babies who are admitted to a neonatal unit and held in the National Neonatal Research Database (NNRD). This data includes background information on the babies (such as how much they weigh at birth), their families (such as any medical problems the mother had during pregnancy), the care they are given (such as medications they are given), and the health problems these babies eventually have (such as infections like sepsis). All information held in the NNRD has had any identifying details removed, so no baby can be identified. This data can be used to better understand this large group of babies, so that we can understand which babies are admitted to neonatal units, and why they are admitted. It can also be used to understand the results of this care by measuring how often these babies have important outcomes (such as death, or blood stream infections, or long-term difficulties with their development). Fully understanding what is happening now to these babies is the first step towards improving the care similar babies are given in the future. In the overarching project this will then be extended to include non-admitted babies and later important outcomes (such as school performance) by linking to data relating to childhood health and education held in other databases.

The engagement work will explore the viewpoints of former patients, families and wider society to the proposed linkage work. For this work to go ahead it is crucial to understand whether it is wanted and acceptable to families and wider society, particularly because given the huge number of babies and mothers whose data will be used it will not be possible to get permission from all of those involved. Instead, the suggested linkage will need approval from regulators: the best way to get this approval is to ensure that this work is co-designed with families from the start, so that it is clearly shown that the work is wanted and needed, and any concerns can be addressed. To understand the views of these groups fully we are going to run focus-groups, an online survey, and targeted interviews. This will allow detailed but broad input from a diverse range of participants to guide the future overarching work.

BENEFITS

This descriptive research will map the care and outcomes given to a neglected group of vulnerable babies and show where this care is not being given according to the best available evidence. The engagement project will make the viewpoints of former patients and families known so that future research can be planned to address their concerns.

This work will also inform the overarching neoOUTCOMES research project which will show how best babies born after 32 weeks should be cared for: this will reduce the inequality that babies requiring early medical care face, helping this large group to thrive.

1.1 BACKGROUND

The first twenty-eight days of postnatal life are crucial to long-term health. In the UK neonatal conditions are responsible for a third of all deaths before the age of 20 and are the leading cause of lost disability-adjusted life years in this population (1). This is in part because neonatal illness is common: one in seven neonates require specialist care, a proportion that continues to increase with time (2, 3). Furthermore, for affected individuals the effects of neonatal conditions can extend throughout the entire life course with increased rates of non-communicable diseases such as ischaemic heart disease, stroke and heart failure seen in adulthood (4, 5). While the most preterm neonates (those born before 28 weeks) are most severely affected, complications such as respiratory issues, sepsis and even intraventricular haemorrhage are seen in moderate or late preterm populations (6). While these complications are rarer for an individual neonate, because so many more neonates are born at later gestations the total number of affected neonates remains high - as is the associated utilisation of healthcare resources (7).

Each year 650,000 neonates are born after 32 weeks, and 90,000 of these neonates are admitted to a neonatal unit (comprising 98% of all livebirths and 90% of all neonatal unit admissions) (8). The average duration of admission in this population varies from 12 days for moderate-preterm (born between 32 and 34 weeks) and late-preterm (born between 34 and 37 weeks) neonates to 4 days for term neonates (8), but as the average cost of a day of neonatal care is £805 (9) the overall annual cost to the NHS can be estimated at £450 million. Many of these initial admissions could be avoided entirely if optimal care was provided in postnatal wards or transitional care (10), while there is unwarranted variation in the care received by admitted (7, 11-16) and non-admitted neonates (17, 18). Given the life-long impact of neonatal illness the unrecognised costs resulting from this suboptimal care provision to neonates born over 32 weeks may dwarf even the considerable burden from initial neonatal admissions in this group.

Furthermore, while the healthcare costs of neonates born after 32 weeks are considerable they are not distributed evenly across the population. It has repeatedly been shown that socioeconomic and ethnic inequalities are responsible for a substantial proportion of preterm births (19-21) and the most deprived neonates go on to have worse outcomes (22, 23). Unfortunately these groups are still least likely to be included in research (24). A recent review of neonatal randomised controlled trials found that only 11% included term neonates, despite this being the largest population group by number (25). The paucity of evidence to guide the care of neonates born after 32 weeks (7, 11, 15, 26) means that care practices show substantial variation (11-14) and are often extrapolated from other groups (26): given the differences in physiology and the conditions that that affect these dissimilar groups this is inadequate to ensure optimal care. Undertaking research in this population also presents specific challenges, beyond those associated with any neonatal research (27). The most important short-term outcomes are rare in this population, meaning that the small sample sizes in most neonatal randomised controlled trials are insufficient to definitively identify the effects of interventions (28, 29). The long follow up periods required to assess developmental outcomes are also challenging (30). Furthermore, evidence synthesis is limited by heterogeneous outcome reporting and poor

methodological quality (25, 31). While there has been a recent focus on reducing term admissions (10), progress in moderate- and late-preterm groups has been more limited. The cumulative effect of these issues means that moderate-, late-preterm, and term neonates are a large, disadvantaged population whose clinical care remains suboptimal due to their underrepresentation in research (7).

Due to the persistent paucity of evidence to guide clinical care in moderate-, late-preterm and term admissions there have been calls to use existing population level data to better characterise this population and their healthcare needs (7). Data about this population is collected during routine clinical care and held in the National Neonatal Research Database (NNRD) (32). It holds deidentified data from all neonates admitted to NHS neonatal units in England, Scotland, and Wales; in total the NNRD contains data from over one million neonates from 2008 to the present and the quality of the data held in the NNRD has been shown to be adequate for research (62). Extracting and analysing this data would allow better understanding of the healthcare needs of this population.

In the future we plan to link this data to childhood health and education data that is routinely collected and held within different databases as part of an overarching research project entitled neoOUTCOMES. This will create a new resource which can then be used to identify non-modifiable and modifiable factors associated with adverse outcomes in this population, and test how modifiable factors affect long-term outcomes such as cognitive ability. Clinical data in the NNRD (32) could be linked with maternal and pregnancy data held in the Maternity Services Data Set (MSDS) (33). Childhood healthcare data is held in the Hospital Episode Statistics (HES) (34) database and educational data is held in the National Pupil Database (NPD) (35). These databases provide population-level data for these groups but are currently fragmented. Linking these data sources will allow the neonatal period to be linked to childhood health and educational outcomes. Similar work has been undertaken for small groups from individual trials (36), and is currently underway for babies born before 32 weeks (37). Undertaking similar linkage in neonates born moderately-, late preterm and at term is essential to optimise the care this population receive, and we will seek the required approvals needed to undertake this work in the future. This overarching work will provide the results needed for future large-scale, prospective, randomised trials to identify optimal care packages. It will be guided by the needs of former patients and parents and will provide a cost-effective approach that will build on ongoing departmental research in similar populations (37).

The overarching neoOUTCOMES work will not be possible without two pieces of pilot work. First, a descriptive study is needed to map the care received by admitted neonates born after 32 weeks, and to explore how the care they receive affects important short-term outcomes using data held within the NNRD. This work can then be extended by subsequent data linkage work to include non-admitted neonates and long-term outcomes. Secondly, a stakeholder engagement project is needed to explore the perspectives of former patients, parents and wider society to the proposed data linkage work. Seeking individual participant consent will not be possible given the size of the population involved and so robust, extensive stakeholder input is essential to demonstrate whether this work is acceptable to all involved so that

regulatory approval from the Confidentiality Advisory Group (CAG) can be obtained. The stakeholder engagement project will also allow a full understanding of how former patients, parents and wider society feel that subsequent work should be conducted so that the neoOUTCOMES project meets their needs and respects any concerns.

The projects described will provide much-needed evidence to guide clinical care and is the first step towards improving outcomes in moderate-, late-preterm and term neonates requiring neonatal care, thereby reducing the health inequalities these groups face.

1.2 RATIONALE FOR CURRENT STUDY

There is a paucity of evidence to guide the medical care given to the 650,000 neonates born each year after 32 weeks, leading to variation in care and outcomes in this vulnerable population. Data linkage is one way to address this gap and identify optimal practice, but to undertake this research in the future preliminary pilot work is required. The descriptive study will allow a full understanding of which neonates are admitted, and identify issues associated with variation in care (suggesting clinician equipoise) which will have important implications for practice in the UK and inform future research in this area. The stakeholder engagement project will identify whether linkage is acceptable to involved participants, and will be critical when seeking regulatory approval for the overarching neoOUTCOMES project. This information will also inform future researchers planning data linkage work in this population.

2. STUDY OBJECTIVES

The proposed pilot projects will provide essential preliminary data required to plan the overarching neoOUTCOMES research project and to allow the attainment of the necessary regulatory approvals.

Study specific objectives:

Descriptive study

- Describe the population of moderate-, late preterm and term neonates admitted to neonatal care in England and Wales.
- Map neonatal admissions in this population by patient factors (such as gestational age and ethnicity) and organisational factors (such as geographic region of birth and level of neonatal unit of admission).
- Identify patient and organisational factors associated with unwarranted variation in patterns of neonatal admission.
- Describe the neonatal core outcomes in admitted moderate-preterm, late-preterm and term neonates.

Stakeholder engagement project

- Describe the perspectives of former patients, parents, and wider society on linkage between existing data to evaluate the impact of neonatal care in neonates born after 32 weeks.

- Identify specific concerns former patients, parents, and wider society have with the proposed linkage work and discuss possible solutions.

3. RESEARCH QUESTIONS

Descriptive study:

- Which neonates born moderately-, late preterm or at term are admitted to neonatal units in England and Wales?
- How do patient and care factors affect rates of admission to neonatal care in moderately-, late-preterm and term infants in England and Wales?
- Which patient and organisational factors are associated with unwarranted variation in rates of admission to neonatal care in England and Wales?
- What are the outcomes of neonatal admission in admitted moderate-preterm, late-preterm and term neonates?

Stakeholder engagement project:

- What are the perspectives of former patients, parents, and wider society on linkage between existing data to evaluate the impact of neonatal care in neonates born after 32 weeks?
- What concerns do former patients, parents, and wider society have with the proposed linkage work and how could they be alleviated?
- Is it acceptable to former patients, parents, and wider society to link perinatal, childhood health, and education data without explicit consent (for the proposed neoOUTCOMES research project)?

4. STUDY DESIGN

Pilot work consisting of two projects:

- Retrospective descriptive epidemiological study using routinely collected data.
- Mixed-methods stakeholder engagement project

5. DESCRIPTIVE STUDY

5.1 DATA SOURCES

This study will use deidentified neonatal care data extracted from the NNRD. The NNRD holds data extracted from point-of-care electronic health records completed by health professionals during routine clinical care. It holds data from all neonates admitted to NHS neonatal units in England, Scotland, and Wales; in total the NNRD contains data from over one million neonates from 2008 to the present. The Neonatal Data Set, a defined national data standard (38) comprising approximately 450 items, is extracted and transmitted to the Neonatal Data Analysis Unit at Imperial College London. The data set includes demographic items relating to mother and baby (e.g.,

gestational age at birth, birth weight, maternal conditions), daily items (e.g., feeding information, medications), care factors (e.g., hospital of birth, transfer during neonatal admission), and discharge items (e.g., diagnoses during admission, weight at discharge). Parents can opt-out if they do not want their child's data to be held within the NNRD. The quality and completeness of the data held in the NNRD has been shown to be suitable for research (39).

Denominator data describing the total number of livebirths by gestational age will be obtained from the Office for National Statistics (ONS) (40) and live births by neonatal network from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) reports (41).

5.2 BACKGROUND VARIABLES

Background variable data will be extracted to allow description of the admitted population of neonates born moderately-, late-preterm and at term. This will include the following:

- Demographic data
  - Gestational age
  - Birth weight
  - Sex
  - Multiplicity
  - Year of birth
  - Ethnicity
- Neonate factors
  - Mode of delivery
  - Apgar score at 5 minutes
  - Chest compressions administered
  - Emergency resuscitation drugs administered
  - Intubated at resuscitation
  - Umbilical cord pH
  - Surfactant administered
  - Admission temperature
  - Admission mean blood pressure
  - Admission blood glucose
  - Admission heart rate
  - Admission oxygen saturation
  - Surfactant administered
  - Mechanical ventilation on Day 1
  - Inotropes administered on Day 1
  - Sepsis suspected on Day 1
  - Transfer on Day 1
  - Admission diagnosis
- Maternal factors
  - Age
  - Gestational diabetes
  - Severe pre-eclampsia requiring pre-term birth

    - Severe pre-eclampsia
    - Gestational hypertension
    - Prolonged rupture of membranes (>24 hours)
    - Suspected chorioamnionitis
    - Receipt of antenatal steroids
    - Receipt of antenatal magnesium sulphate
- Organisational factors
    - Level of initial neonatal unit
    - Neonatal network

These variables will allow the population of moderately-, late-preterm, and term neonates admitted to neonatal units to be described fully. It will also allow the identification of patient and organisational factors that affect the rate of neonatal admission in different groups, with adjustment for confounding factors.

5.3 OUTCOME MEASURES

To measure the results of admission in moderately-, late-preterm and term neonates data on the following neonatal core outcomes (42) will be extracted:

- Survival to discharge home; defined as recorded as alive at final neonatal unit discharge.
- Late Onset Sepsis; defined in line with the Royal College of Paediatrics and Child Health National Neonatal Audit Programme (NNAP) definition “pure growth of a pathogen from blood” or “pure growth of a skin commensal” or a “mixed growth” after the first 72 hours of life (43)
- Necrotising enterocolitis; defined using the NNAP definition (43)
- Brain injury on imaging; defined in line with the UK Department of Health definition of neonatal brain injury (44)
- Retinopathy of prematurity; defined as a record of any retinopathy of prematurity on routine screening in the National Neonatal Dataset “retinopathy of prematurity ad-hoc form”
- Bronchopulmonary dysplasia; defined using the NNAP definition (43) of significant bronchopulmonary dysplasia.

Long term outcomes after discharge will also be measured:

- Blindness; defined as an answer of Yes to the question “Does this child have a visual impairment?” on the NNAP form (43)
- Deafness; defined as an answer of Yes to the question “Does this child have a hearing impairment?” on the NNAP form (43)
- Ability to walk; defined as an answer of Yes to the question “Is this child unable to walk without assistance?” on the NNAP form (43)

It will not be possible to measure the following components of the core outcomes set: adverse events, quality of life, gross motor ability, or cognitive ability as relevant data are not captured in the NNRD.

These outcomes will allow the results of neonatal care in moderately-, late-preterm, and term neonates admitted to neonatal units to be described fully.

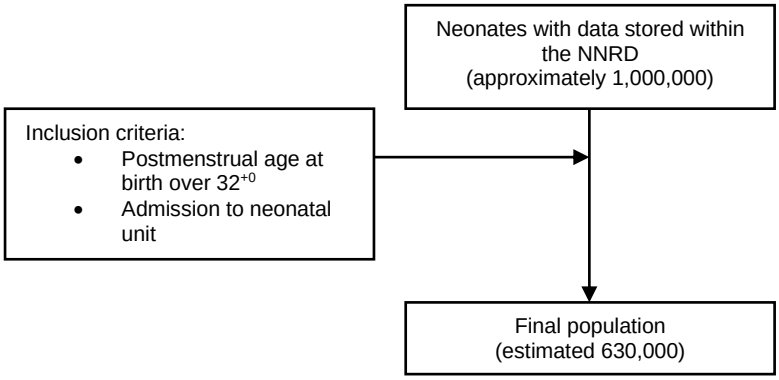
5.4 PARTICIPANT ENTRY: INCLUSION CRITERIA

Neonates born after 32^{+0} weeks^{+days} postmenstrual age between 1st January 2015 and 31st December 2022 and admitted to a neonatal unit in England and Wales).

5.5 PARTICIPANT ENTRY: EXCLUSION CRITERIA

No neonates will be excluded from this descriptive analysis.

5.6 PARTICIPANT ENTRY: STUDY FLOW CHART



5.7 DATA ANALYSIS: DESCRIPTIVE ANALYSIS OF ADMISSIONS

We will describe the population of moderately-, late preterm and term neonates admitted to neonatal units in England and Wales. We will describe the total number of neonates admitted each year in each gestational age category and birth weight category, using WHO definitions (45, 46). We will also describe the causes of admission, identifying the most common five diagnoses in each group.

5.8 DATA ANALYSIS: FACTORS AFFECTING RATES OF ADMISSION

We will explore how rates of neonatal admission are affected by neonatal and organisational factors. Using ONS and MBRRACE-UK data as denominator data we will compare rates of neonatal admission by the following factors:

- Gestational age (grouped by WHO definitions)
- Ethnicity
- Geographic region (with neonates grouped by neonatal network of birth)
- Level of initial neonatal unit

The significance of differences in rates of admission, compared to the national average, will be tested using the Student's t-test. To avoid issues arising from multiplicity within each factor we will use the Bonferroni-Holm correction (47). Variation in rates of admission will be considered unwarranted if it meets the following accepted definition: patient care that differs in ways that are not a direct and proportionate response to available evidence; or to the healthcare needs and informed choices of patients (48).

5.9 DATA ANALYSIS: DESCRIPTIVE ANALYSIS OF NEONATAL CORE OUTCOMES

We will describe the neonatal core outcomes across the entire population of moderately-, late-preterm, and term neonates admitted to neonatal units in England and Wales. We will report the overall rates of survival, short-term neonatal core outcomes and long-term neonatal core outcomes. The rates of each outcome will also be reported by gestational age category. In keeping with similar work using this dataset (13) we anticipate significant amounts of missing data for the long-term outcomes: if the amount of missing data is greater than 10% we will not analyse the data further due to the risk of bias (49) and will only report the proportion of missing data as this will inform future research.

5.10 DATA ANALYSIS: SUBGROUP ANALYSES

No further subgroup analyses are planned at this time: any post-hoc subgroup analyses that are conducted will be clearly reported as such with due caution in the interpretation of findings (50, 51).

5.11 DATA ANALYSIS: SAMPLE SIZE

Since 2008 the NNRD holds data on approximately one million babies. Around 90,000 moderately-, late-preterm, and term neonates are admitted to neonatal units in England and Wales each year. Over the study period we will have a population of around 630,000 admitted neonates. Given that the mean admission rate in this group is 14% (with an estimated variance of 0.12) our sample size will give a power of 1.00 to detect a 5% absolute difference in admissions in groups as small as 10% of the total population (allowing for correction for multiple comparisons).

6. STAKEHOLDER ENGAGEMENT PROJECT

6.1 METHODS

Three stage mixed-methods approach. First, four focus groups will be completed to discuss the project, the need for data linkage to improve neonatal outcomes, and to co-create an online survey. Then participants will be recruited to complete the co-created online survey exploring family perspectives to retrospective linkage of neonatal, child-health and education databases. Finally, in-depth interviews will be held with survey participants who express negative views on the proposed linkage work to better understand potential barriers.

6.2 METHODS: FOCUS GROUPS

For the four focus groups twenty-four participants will be recruited for four separate focus groups, which will be facilitated by two researchers. Participants will be recruited through the project website and social media (disseminated via charity partners). Participants will include former neonates born after 32^{+0} $weeks^{+days}$, parents (including mothers, fathers, parents of admitted neonates, and parents of neonates who did not require admission), healthcare professionals, and representatives of wider society. Participants will be selected purposively to include a broad range of background (including a range of ethnicities, educational statuses, and degrees of deprivation). Time will be allocated for discussion of the scope of the project, the need for data linkage to improve neonatal outcomes, concerns relating to proposed linkage and any other issues raised by participants. Participants will be asked whether they feel it is appropriate to use data linkage without explicit consent for the proposed neoOUTCOMES research project. Participants will also review the proposed national survey to ensure it is tailored to the needs of the target audience. Focus groups sessions will be recorded and transcribed. Four focus groups should be sufficient to achieve the project aims and was found to be sufficient to reach saturation (52).

6.3 METHODS: ONLINE SURVEY

For the online survey participants will be recruited nationally (via the project website and social media disseminated via charity partners) to complete the co-created online survey exploring family perspectives to retrospective linkage of neonatal, child-health and education databases. The survey will be created using the Qualtrics online survey tool. Participants will include former neonates born after 32^{+0} $weeks^{+days}$, parents (including mothers, fathers, parents of admitted neonates, and parents of neonates who did not require admission), healthcare professionals, and representatives of wider society. This will include targeted recruitment of

underrepresented groups (including minority ethnicities and economically disadvantaged groups). Participants will also be asked whether they would be prepared to participate in subsequent in-depth interviews. Deidentified survey responses will be analysed via SPSS.

6.4 METHODS: IN-DEPTH INTERVIEWS

For the in-depth interviews ten individuals will be identified from the online survey who did not feel that the use of data linkage was appropriate. Cases will be purposively identified to provide a range of backgrounds among those invited to participate in individual interviews. These will be organised online or face-to-face (whichever is more convenient for the participant). Given that previous similar work showed that opposition to data linkage was unusual six interviews should be sufficient and will avoid unnecessary replication (52), but if data saturation has not been reached then further interviews will be held. All interviews will be recorded and transcribed.

6.5 DATA ANALYSIS

A mixed methods thematic analysis will be undertaken incorporating the focus group transcriptions, online survey results and interview transcripts to identify and illustrate overarching themes. Anonymised data will be coded by two independent researchers using an iterative approach, with any disagreements resolved by a third researcher.
All stages will be reported in line with the Consolidated Criteria for Reporting Qualitative research (53).

7. REGULATORY ISSUES

7.1 RESEARCH ETHICS APPROVAL

The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee approval (16/LO/1093), and Confidential Advisory Group approval (ECC 8-05(f/2010)), to form the NNRD. Standalone approval will be sought from the national research ethics service for the pilot projects described. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 CONSENT

For the descriptive study no patient consent will be required as only de-identified data from the NNRD will be used.

For the stakeholder engagement project informed consent will be obtained from all participants.

7.3 DATA PROTECTION AND CONFIDENTIALITY

All investigators and study site staff will comply with the requirements of the Data Protection Act and the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles. Imperial College London will act as the data controller for these pilot projects. Data from this project will not be transferred internationally and identifiable data will not be shared with other third parties: deidentified data may be shared with other researchers when appropriate.

For the descriptive study only de-identified data will be used. Imperial College will collect information for this research study from the Neonatal Data Analysis Unit. The Neonatal Data Analysis Unit will not provide any identifying information to Imperial College. We will use this information to complete the described research.
As no patient identifiable data will be used in the descriptive study HRA Confidentiality Advisory Group approval is not required.

Data from the NNRD will be extracted by staff from the Neonatal Data Analysis Unit operating within the guidelines established by Research Ethics Committee approval (REC Reference: 16/LO/1093) and Confidentiality Advisory Group approval (CAG reference: ECC 8-05(f)2010). No member of the study team will have access to identifiable data on any study participant: they are not part of the clinical care team. Data for this work will be extracted from the NNRD. The NNRD is an established research database and holds National Research Ethics Service approval (16/LO/1093). Data held within the NNRD will be retained as a research database. A copy of the study data extract will be retained by the NNRD as part of the research database.

During the stakeholder engagement project personal email addresses for communication with prospective participants (in the focus group and interview stages) and participants (in all stages) to communicate with the study team. Communications from the study team will be sent from a secure NHSmail account. Email addresses will be considered sensitive information and stored securely on a password secured computer in a locked office on the Chelsea and Westminster Hospital Campus of Imperial College London. Direct quotations from respondents will be published as part of the reports for the stakeholder engagement project (including responses from the focus groups, online survey and interviews). All quotations will be anonymised fully, and quotations containing identifiable data will not be used. For the descriptive study only de-identified data will be used. All study data will be stored on a password secured computer in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for 10 years in line with institutional policy. For the stakeholder engagement project personal data will include names, ethnicities, postcode and highest educational attainment. The name, ethnicity, postcode and highest educational attainment data for participants will be stored on an encrypted file on a password secured computer in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. The name data will also be stored on paper copies of the participant consent forms: these will be filed in a locked filing cabinet in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for 10 years in line with institutional policy. For the stakeholder engagement project electronic data will be stored on an

encrypted file on a password secured computer in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. Only the study investigators (Dr James Webbe, Dr Cheryl Battersby and Prof Chris Gale) will have access to this file. Paper copies of participant consent forms will be filed in a locked filing cabinet in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. This will be accessible only by the Principal Investigator (Dr James Webbe). All data will be stored for 10 years in line with institutional policy.

For the descriptive study only de-identified data will be used. All study data will be stored on a password secured computer in a locked office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for 10 years in line with institutional policy.

7.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 FUNDING

The funding for creating and maintaining the NNRD is from unrestricted funding awarded to Prof Neena Modi. This funding includes costs involved in data transfer, storage, cleaning, merging, administration and regulatory approvals. The extraction of study data from the NNRD is funded through funds awarded to Prof Gale as part of a Medical Research Council (MRC) Clinician Scientist grant. Data analysis funded as part of a National Institute for Health and Care Research (NIHR) Clinical Lecturer grant awarded to Dr Webbe. Stakeholder engagement work funded by a charitable grant from CW+ awarded to Dr Webbe.

7.7 DATA STORAGE

All data will be stored on a password secured computer in the Clinical Research Fellow's Office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for ten years. Deidentified data can be accessed, upon reasonable request, by contacting the primary investigator.

7.8 AUDIT

The study may be subject to 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.

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Section of Neonatal Medicine at Imperial College London. Monitoring and auditing research conduct will be performed by the sponsor as required and according to the sponsor's standard operating procedure.

9. PUBLICATION POLICY

The results of these pilot projects will be reported in manuscripts in peer-reviewed scientific journals. All members of the study group will be authors with additional contributors as appropriate. JW will be first author, CG will be last author. The UK Neonatal Collaborative will be named collaborators and will be acknowledged in all academic publications.

To maintain confidentiality during publication of the descriptive study no identifiable personal data will be used. For the stakeholder engagement project no identifiable data will be published. Information on participants in the focus groups, online survey and interviews will only be presented in aggregate form so it will not be possible to identify individual participants from the publication. Direct quotations will be anonymised and no quotation involving personal data will be used.

To inform participants of the study results the descriptive study results will be made available through the Health Data Research UK Gateway webpage, in line with projects utilising data from the National Neonatal Research Database. The results of the stakeholder engagement project will be shared with participants by email (with prior consent from the participants). A two page plain English summary of the study findings will be written in collaboration with the former neonatal patients and parents on the project steering committee. This dissemination plan was created in collaboration with the former patients and parents on the project steering committee.

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