

ROYAL WOLVERHAMPTON NHS TRUST

**OPTI-PREM: OPTIMISING NEONATAL SERVICE PROVISION
FOR PRETERM BABIES BORN BETWEEN 27 AND 31 WEEKS OF GESTATION
USING NATIONAL DATA, QUALITATIVE RESEARCH AND ECONOMIC ANALYSIS**

Detailed project description NIHR grant Full Application 15/70/104

SHORT TITLE: OPTI-Prem

SPONSOR : Royal Wolverhampton NHS Trust

**RESEARCH ETHICAL APPROVAL : IRAS: 212034
Clinicaltrials.gov database - NCT02994849**

COLLABORATING UNITS

**University of Leicester
University of Oxford
Imperial College
Neonatal Data Analysis Unit
BLISS Premature Baby Charity**

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DETAILED PROJECT DESCRIPTION

OPTI-PREM: OPTIMISING NEONATAL SERVICE PROVISION FOR PRETERM BABIES BORN BETWEEN 27 AND 31 WEEKS OF GESTATION IN ENGLAND USING NATIONAL DATA, QUALITATIVE RESEARCH AND ECONOMIC ANALYSIS

SCIENTIFIC SUMMARY

The overarching aim of the project is to improve neonatal service delivery for babies born between 27 and 31 weeks of gestation in England, by providing evidence-based data for the development of national policy, on the optimal place of care for such babies. Endorsed by the neonatal advisory body within the Royal College of Paediatrics and Child Health, the British Association of Perinatal Medicine (BAPM), the Neonatal Clinical Reference Group (CRG) and the UK parent support group and charity for sick and preterm babies (BLISS) the study outcomes will be used to produce national recommendations, which will be used to guide the commissioning and delivery of future neonatal health services in England.

There are three types of neonatal units providing care for newborn babies in England: Neonatal Intensive Care Unit (NICU); Local Neonatal Unit (LNU); and Special Care Baby Unit (SCBU). Babies of 27 to 31 weeks gestation at birth are usually born and managed in a NICU or a LNU, rather than a SCBU. NICUs can provide higher intensity care than LNUs, but both have facilities to support babies born at <32 weeks of gestation, whereas most SCBUs do not. Current practice makes no distinction between care delivered in either a LNU or NICU, as these babies do not all require the highest intensity of care. The decision on where individual babies are born is based on maternal choice at booking, presentation to the nearest hospital and cot capacity at the time of delivery. However, these two types of neonatal unit differ in terms of facilities, staffing and staff skill mix for the care of preterm babies.

Significant new evidence shows that care in a NICU, as opposed to a LNU, has benefit in terms of improved survival to discharge; this is shaping policy for this group in England. In contrast, there is no evidence to guide the location of care for the next most vulnerable group of babies born just above 26 weeks, up to 31 weeks of gestation (hereafter called 27-31 weeks), and their care is currently spread between 45 NICUs and 84 LNUs. This is an important group to target; they account for ~4 fold more throughput into neonatal units compared to those born at 23-26 weeks, and make up 12% of all preterm babies born in England. In 2014, they utilized twice as many neonatal bed days/year in the NHS compared to the group of babies born at 23-26 weeks (304 893 vs 147 225; NDAU unpublished data); this comprised over a third of all care days offered to all babies in neonatal units in England.

Our research will determine whether the type of unit in which neonatal care is delivered influences outcomes for these babies. It is important to know whether the benefits of NICU care in relation to survival and morbidities that have already been identified for babies born at 23-26 weeks, also extend to babies born up to 31 weeks. It will also address whether it is safer and more cost-effective for particular groups of babies (according to gestational age and/or clinical condition) within the gestational age range 27-31 weeks to be cared for in LNU, and whether there is a set point in gestational age within this range at which care can be equitably provided between LNUs and NICUs. It is also important to understand service user perspectives on place of care for these babies, as these will also drive recommendations to be developed.

The primary objective will be to assess, for preterm babies born at 27-31 weeks and admitted to a neonatal unit, whether care in a NICU compared LNU impacts on survival and other key morbidities,

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at each gestational age in weeks. Within this we will also assess the impact of postnatal transfers between neonatal units (after day 1 of life) on gestation-specific survival and major morbidities. The time horizon for outcomes (survival and major morbidities) will be up to one year of age. Our secondary objectives will be to assess whether there are key differences in clinical care provided in LNU vs NICU, and if so, whether these differences are associated with gestation-specific differences in outcomes; parents' and clinicians perspectives regarding place of care, and how these can be used to guide decision making on place of care.

This will be conducted as a 3 year study involving five work streams to address each objective:

1. A Clinical Outcomes Study: Statistical analysis using data routinely collected from the NNRD for all births at 27-31 weeks gestation admitted to neonatal care and who died on or were discharged from neonatal units between 01/01/14 and 31/12/17, in England; with linkage to Hospital Episode Statistics and Office for National Statistics databases to determine gestation specific survival and morbidities up to 1 year of age.
2. A Study on Clinical Care addressing differences in care between neonatal units that may impact on neonatal outcomes
3. An Economic Analysis of care provided between LNU and NICU, within the NHS setting
4. A Qualitative, social ethnographic study: with parents and clinicians, exploring service user perspectives on place of care for this group.
5. Establishment of a working group in collaboration with the British Association of Perinatal Medicine to set framework documents and national recommendations on place of care. These will be used to inform commissioning for health service delivery nationally.

BACKGROUND AND RATIONALE

Introduction

Specialised services for neonates in England are delivered by neonatal units managed through Operational Delivery Networks. Neonatal units are categorised as Neonatal Intensive Care Units (NICUs) Local Neonatal Units (LNUs), and Special Care Baby Units (SCBUs)¹. NICUs are located within centres that have specialist obstetric and feto-maternal medicine services; they have staff and resources to provide tertiary level care for babies of all gestational ages with a wide range and complexity of conditions. LNUs provide care for babies within their local catchment area; they are able to provide emergency, short-term intensive care but are not resourced to provide long-term intensive care; they generally focus on babies who do not demand the very highest intensity of care². SCBUs provide the lowest intensity of care, ideally close to the family home, and generally care for babies born >32 weeks gestation.

Recent evidence from the UK indicates^{3,4} that, for babies born at 23-26¹ weeks of gestation, management in a NICU confers significant benefit in terms of improved survival to discharge; this knowledge is now shaping policy for these babies⁵. In contrast to this and other extensive data available on these extremely preterm babies, there is no evidence to guide the location of care for the next most vulnerable group of babies born between 27⁺⁰ weeks and 31⁺⁶ weeks of gestation (hereafter called 'born at 27-31 weeks'). This is now an important group to target; they account for around four times the throughput in neonatal units when compared to those born at 23-26 weeks

¹ Babies born at 22 weeks and under are generally not considered viable

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gestation (Figure 1 a and b), and for up to 12% of all viable preterm babies born in England in 2013 (6242/51000)⁶. Currently these babies are cared for in either LNUs or NICUs, and those who are inadvertently born in a hospital with a SCBU are transferred to a hospital with a LNU or NICU for continued care. In 2014, 5991 babies were born at 27-31 weeks of gestation in England. Their care was spread between NICUs (48%) and LNUs (41%) [Neonatal Data Analysis Unit (NDAU) unpublished data, Figure 1a]. They were cared for over 304 893 days/year on neonatal units in England. This is double that utilised by those born at 23-26 weeks, and constitutes over a third of all care days offered to babies in neonatal units in England in 2013 and 2014 (Figure 1a).

a)

Category	2013	2014
Total Admissions		
≤26 weeks	1804	1731
27-31 weeks	6046	5991
Survival to discharge from NNU		
≤26 weeks	1345	1258
27-31 weeks	5789	5710
Total days in hospital *		
≤26 weeks	146226	147225
27-31 weeks	306618	304893
All Other NNU admissions	590854	611687

b) Number of infants by birth weight category and gestational age category in the National Neonatal Research Database by final neonatal discharge year, including infants discharged between 1st January 2014 - 31st December 2014

Birth weight category (in grams)	Number of infants (% of all infants)	Gestational age category (in completed weeks)	Number of infants (% of all infants)
≤ 999 g	2,668 (3)	≤ 25 weeks	1,144 (1.3)
1000 – 1499 g	4,712 (5.2)	26-32 weeks	9,637 (10.7)
1500 – 1999 g	9,400 (10.4)	33-36 weeks	24,770 (27.4)
2000 – 2999 g	30,848 (34.2)	≥ 37 weeks	54,674 (60.6)
≥3000 g	37,852 (47.2)	Missing	28 (0.0)
Missing	22 (0.0)		
Total	90,253	Total	90,253

Figure 1: a) Babies recorded on the National Neonatal Research Database (NNRD): 27-31 weeks vs ≤26 weeks in England 2013-2014 (NDAU unpublished data). * These include all babies, including those who had died on a neonatal unit in England. b) Published figures from NDAU⁷ for 'equivalent gestations' in England and Wales; there are no data published comparing throughput between ≤26 and 27-32 weeks in England.

Most networks have defined a cut-off gestational age, below which they aim to provide care in a NICU^{2,8}. However, these criteria differ between networks, are not evidence-based and are often not adhered to. Currently, since both NICUs and LNUs are able to provide care, care pathways for babies born at 27-31 weeks are undefined and their management is spread, often arbitrarily between NICUs and LNUs. Our research will determine whether the type of unit in which neonatal care is delivered influences outcomes for these babies. It is important to know whether the benefits of NICU care in relation to survival and morbidities that have already been identified for babies born at 23-26 weeks also extend to babies born up to 31 weeks. It is also important to know if it is safer and more cost-effective for particular groups of babies (according to gestational age and/or clinical condition) within the gestational age range 27-31 weeks to be cared for in LNUs, and whether there is a set point within this gestational age range at which care can equitably be provided in either LNUs and NICUs.

Preterm babies born at 27-31 weeks gestation

Health care burden: Preterm birth (<37 weeks) generates a substantial health care burden, initially during the neonatal hospital stay, and subsequently through increased risks of long-term neurodevelopmental, cognitive, behavioural and physical health problems⁹. Babies born at 27-31 weeks of gestation comprised ~12% of all UK preterm births in 2013⁶ and numbered 12 037 in England and Wales in 2013-14 (NDAU, unpublished data). In 2014 their in-hospital neonatal mortality was 30 per 1000 neonatal unit admissions (unpublished data NDAU, 2014 181 deaths/5991 admissions), and their infant mortality rate ranged from 110/1000 live births at 27 weeks gestation, to 26/1000 live births at 31 weeks gestation, in 2013⁶. These babies spend a median of 44 days in hospital, and are discharged at a median of 36.4 days corrected gestational age⁷.

Health economic impact: The cost of care for preterm babies in England and Wales was estimated at £2.946 billion in 2006¹⁰⁻¹¹. Detailed cost analyses for births at 27-31 weeks gestation have not

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specifically been described, but recent literature suggests that healthcare costs decline as gestational age from extreme to moderate-late prematurity increases^{10,12}. Survival in babies born at 27-31 weeks gestation has improved in recent years. Hospital costs are high, with specialised neonatal intensive care in the range of £776-£1120 per day and high dependency care £709-£983 per day, depending on the Neonatal Network in which care is delivered. Therefore it is important to ensure both that care for less sick preterm babies is not unnecessarily located within a NICU, and that sicker preterm babies are not under-supported in a LNU, potentially resulting in prolonged intensive care and greater short- and long-term morbidity. However, if key clinical outcomes do not significantly differ between LNUs and NICUs, then cost-effectiveness and family satisfaction should be the major drivers for how and where health services are delivered in this population.

Current management: Currently, there is no evidence-based guidance on the optimal place of neonatal care for babies born at 27-31 weeks gestation, nor well-defined care pathways, and their care is spread across the 45 NICUs and 84 LNUs in England and Wales. Whilst the type of care provided by LNUs and NICUs overlaps considerably, the complexity of problems that can be managed differs between the two. We do not know if some babies, such as those more preterm or sick, may benefit from care in a NICU that can manage the most complex conditions and complications, or whether others, less sick or more mature, may benefit more from care in a LNU, geared towards lower intensity care, closer to home.

At present, the chief determinant of where babies born at 27-31 weeks gestation are cared for is the hospital where the mother is booked for her antenatal care, which may be in a maternity centre that has NICU, LNU or SCBU facilities. This is usually the centre closest to her home and is not necessarily determined by the anticipated degree of illness or complexity of care required for either mother or baby. This is partly because, for most women at the time of booking for pregnancy care, the risk of pregnancy complications and/or preterm delivery is unpredictable. A further determinant is cot availability for care of the baby. Transfers between hospitals are frequent, whether for a mother before delivery, or for her baby after birth, and are determined not only by care requirements, but also by cot capacity and adequacy of neonatal nurse and medical staffing.

Clinical profile: Babies born at 27-31 weeks gestation do not always represent the sickest of the preterm babies and the effects of immaturity *per se* are often less profound in this group compared to those on the threshold of viability (23-26 weeks). Unless considered non-viable on delivery suite, babies of 27-31 weeks are *always* admitted to a neonatal unit for care, as they are too immature for immediate transfer home or for routine care in a postnatal ward. They are a heterogeneous group, with birth in this range being associated with varying but substantial adverse outcomes and differing mortality for each week of gestational age⁶, and a group in which the most appropriate care pathways are intuitively likely to yield the greatest benefits for cost-effectiveness, clinical outcome and health service delivery. While there is some information about gestation-specific mortality⁶, there are very limited data on gestation-specific morbidities. Many previous studies that have included babies born at 27-31 weeks were conducted many years ago, and were designed to clarify the effects of very low birth weight rather than prematurity. It is now accepted that the outcomes of preterm birth are more appropriately characterised by degree of immaturity.

Preterm babies born at 27-31 weeks have shown a relatively greater increase in survival over the past two decades compared with less mature babies¹³. The North of England recorded a ~50% reduction in mortality between 2002 and 2008 compared with 1988-1994 in those born at 28-31 weeks of gestation¹⁴; trend data also indicates substantial survival gains in other countries such as Sweden¹⁵ and the USA¹⁶ over previous decades. This increase in survival not only places increasing demands

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on neonatal services, but is also likely to have led to changes in the profile of neonatal morbidity, hospitalisation and outcome, the details of which have not yet been captured by UK studies.

Clinical care pathways: The main driver for neonatal care pathways in the UK comes from gestation-specific analyses for preterm babies born at 23-26 weeks. There are no data to inform the optimal location of care for preterm babies born at 27-31 weeks, in relation to mortality and morbidities. Although there is some evidence to suggest that mortality and morbidity profiles (based on common major morbidities - necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) for the *total group* of babies born at 27-31 weeks gestation⁴ is similar between LNUs and NICUs, it remains unknown whether location of care makes a difference to *gestation specific* outcomes and there is no defined care pathway for this group.

Parent and clinician perspectives: There are minimal data on parental perspectives on place of care in the UK. The initial rationale driving the configuration of neonatal networks in England and Wales was centralisation to improve outcomes. This inevitably results in many babies who will be cared for in neonatal units far away from their family home. These may include preterm babies who are ill and require intensive care or surgical facilities, or are more mature and well, but required to move within their Network agreed pathways of care, for cot capacity reasons. Transfers between neonatal units are stressful for parents and often incur additional travel costs for the family. The logistics of arranging a transfer, coupled with parental anxieties about either a sick baby or a stable baby who must move because the neonatal unit in the centre of birth is full also make this a stressful process for staff. These factors may influence decisions about where and whether a baby is transferred. Both clinical and parental perspectives are important in reaching a decision about the optimal location of care. Taking these perspectives into account will help ensure provision of care that is as parent/family-centred as possible, and meet the objectives set by the DOH Toolkit², NICE Quality Standards⁸ and more recently, the Top Priorities for Research set through the NIHR funded James Lind Alliance¹⁷.

Conclusions: Preterm babies born at 27-31 weeks gestation are a vulnerable, heterogeneous group, with a high mortality rate in the neonatal period and infancy. Currently in the UK they are predominantly cared for in either LNU or NICU, but the optimum location has not been defined. Unlike their more immature counterparts, there are no gestation-specific data detailing their mortality and morbidity when managed in LNU compared to NICU. The healthcare costs for these babies and social aspects of care relating to place of birth are unknown.

WHY IS THIS RESEARCH NEEDED NOW?

Preterm births are increasing and with advances in obstetric and neonatal care, survival is improving. Preterm babies impose a large and growing burden for the NHS, and their neonatal care is among the top three high cost specialised NHS services. Research into prevention of preterm birth has so far been unable to reduce rates substantially. A cardinal focus is to optimise the quality and cost-effectiveness of care and minimise short and long term adverse consequences for babies, their families and the NHS. This research would meet a number of current needs:

1. *Response to new evidence about outcomes associated with place of neonatal care for preterm infants:* Place of care has recently been associated with improved outcomes for the most preterm babies and it is now known that those born at 23-26 weeks have better survival when managed in a

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NICU/high volume neonatal unit^{3,4}. Babies born at 27-31 weeks of gestation are also a high risk group, carrying substantial risk of neonatal mortality and morbidity and long-term adverse outcomes. However, for this group there is paucity of research data. Epidemiological work across the spectrum of prematurity has shown a gradient of increasing risk extending from the least to the most preterm^{2,18}. Whilst this effect is increasingly acknowledged, no study has focused on the heterogeneous 'middle' group some of whom resemble their sicker, smaller counterparts and some the more mature group. Outcomes of babies born at 27-31 weeks of gestation are therefore unknown and may be compromised by inappropriate models of care. It is likely that some are receiving more intensive intervention than is necessary and others, receiving less intensive care than is desirable. There is a pressing need to optimise quality of care for these babies.

2. *Configuration of neonatal services:* The potential benefits and challenges of centralisation of neonatal care are the focus of discussions about provision of neonatal services in England. These are largely based on existing research from the EPICure studies of babies born at 23-26 weeks. To fully inform these important dialogues, there is a need to identify which types of neonatal units provide optimal care for babies born at 27-31 weeks, who may now constitute a larger burden than those born at 23-26 weeks.

3. *Optimising cost-effectiveness of neonatal care:* The current financial constraints within the NHS provide a compelling reason to seriously explore areas of potential saving in models of delivery of care. As a group preterm babies have much higher associated costs than term babies, most of which arise through inpatient services during the birth admission¹¹. The throughput into neonatal units, for babies born at 27-31 weeks is approximately 4 fold greater than those born at 23-26 weeks, and their care makes up a third of the care in days provided for all neonates in England (Figure 1a, NDAU unpublished data). However, for this larger group, relatively little is known about the costs of care, which is distributed between LNUs and NICUs. Differences in facilities, resources and staffing means there are likely to be inherent differences between LNUs and NICUs in costs and in the way in which care is provided for babies with similar problems at similar gestational ages. Little is known about the impact of such variation on short- or long-term outcomes, and as a result accurate cost-effectiveness estimates are needed to optimise neonatal service delivery. This is now emerging as a key area for consideration, with potentially significant cost savings for the NHS.

4. *Partnerships between parents and clinicians:* Ever-increasing importance is being placed on service user involvement in decision making within the NHS and this is now an expectation of the general public. Partnership with parents in decision making about their infants' care following preterm birth is important, but their voices have not as yet been effectively heard. Both parents and clinicians have important insights as a result of their experience in navigating this complex and sensitive health care setting. Many parents whose babies have been delivered at 27-31 weeks of gestation will have experienced maternal antenatal transfer or postnatal transfer of the baby, with the associated psychological and financial costs. We must ensure that such experiences are effectively captured and used to help optimise service delivery for preterm babies that is acceptable to and supportive of families.

5. *The need for national guidance:* There is substantial variation between units and neonatal networks in the way that care is provided for babies born at 27-31 weeks of gestation. National recommendations from professional bodies would provide the necessary guidance but must be based on robust evidence, which does not currently exist. Our research proposal is supported by the British Association of Perinatal Medicine (BAPM), the Royal College of Paediatrics and Child Health, BLISS, the UK charity for sick and preterm babies, and the Neonatal Clinical Reference Group (CRG) of NHS England. The project will include developing, with them and other relevant stakeholders such as

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Neonatal Networks, Neonatal Nurses, Royal College of Nursing, and Commissioners including Neonatal Specialist Commissioners, recommendations based on the study findings and promoting implementation of these recommendations. The results of this project will therefore shape health services and delivery of care based on research that benefits the preterm baby, and is considerate of parental, clinician and economic needs.

AIMS AND OBJECTIVES

AIM: The overarching aim of our research is to optimise neonatal service delivery for babies born at between 27⁺⁰ to 31⁺⁶ weeks of gestation ('born at 27-31 weeks').

OBJECTIVES:

Our primary objective is to address the research question:

1. For preterm babies born at 27-31 weeks of gestation (population) and admitted into a neonatal unit for care, does care in a NICU (intervention), when compared to care in a LNU (comparator) result in improved gestation specific survival (primary outcome) and reduced major morbidity (secondary outcomes) up to 1 year of age?

We will assess, within this primary objective, the impact of postnatal transfers between neonatal units (after day 1 of life) on gestation-specific survival and major morbidities up to 1 year of age.

Our secondary objectives are to determine:

2. For preterm babies born at 27-31 weeks gestation and admitted into a neonatal unit for care:
 - a) whether there are key differences in clinical care provided in LNUs vs NICUs, and whether any identified differences are associated with gestation-specific differences in outcomes;
 - b) where it is most cost-effective to care for these babies from NHS perspective (LNU or NICU);
 - c) parents' perspectives regarding place of care, and how these can be used to guide decision making on place of care;
 - d) LNU and NICU clinicians' perspectives regarding place of care, and how these can be used to guide decision making on place of care.

We will use the study findings as a basis for discussions with the BAPM, the Neonatal Clinical Reference Group (CRG), Neonatal Specialist Commissioners BLISS and relevant stakeholders such as Neonatal Nurses and Newborn Networks, in order to

- develop recommendations on the optimal, most cost-effective place of care for these babies, and
- promote implementation of these recommendations

We have the support of the BAPM, BLISS, the Royal College of Paediatrics and Child Health (RCPCH) and the Neonatal CRG for this work.

RESEARCH PLAN/METHODS

This mixed methods, longitudinal study will comprise five work streams, underpinned and supported by a BLISS Parent Advisory Panel of 10 parents led by a Parent Advisory Panel Chairperson, throughout (see flow diagram, Figure 2). This panel represents a diverse mix of mothers and fathers from around the country, and includes parents of minority ethnicity, parents with previous preterm births, parents who have experienced a preterm neonatal death, and those who have been managed in LNU, NICU as well as transferred between LNU and NICU. A detailed analysis plan will be agreed with the Study Steering Group, comprising all the co-applicants, including the Parent Advisory Panel Chair, at an early stage, before all of the data have been collected, and any subsequent amendments

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will be clearly stated and justified. The Study Management Group, responsible for the day to day co-ordination of the study will be formed by the Chief applicant T Pillay [TP], and her research assistant, supported by mentors E Boyle [EB] and N Modi [NM]. The five work streams are:

Work stream 1. Clinical Outcomes Study (To address the Primary Objective)

Study Population:

a) *In-patients up to discharge from Neonatal Unit:* We will obtain data from the National Neonatal Research Database (NNRD) on admissions to neonatal units in England for babies born at 27-31 weeks of gestation, between 01/01/14 and 31/12/2017. The NNRD is a national resource developed and managed at the Neonatal Data Analysis Unit (NDAU), Imperial College London. It contains patient-level data extracted at quarterly intervals from the real-time, point-of-care, clinician-entered electronic records of all NHS neonatal units in England, Wales and Scotland (N=200). Data currently available is of high quality and completeness. However, for the purposes of reassurance for this study, further robustness of the data will be ensured by adding a feedback loop (Appendix I).

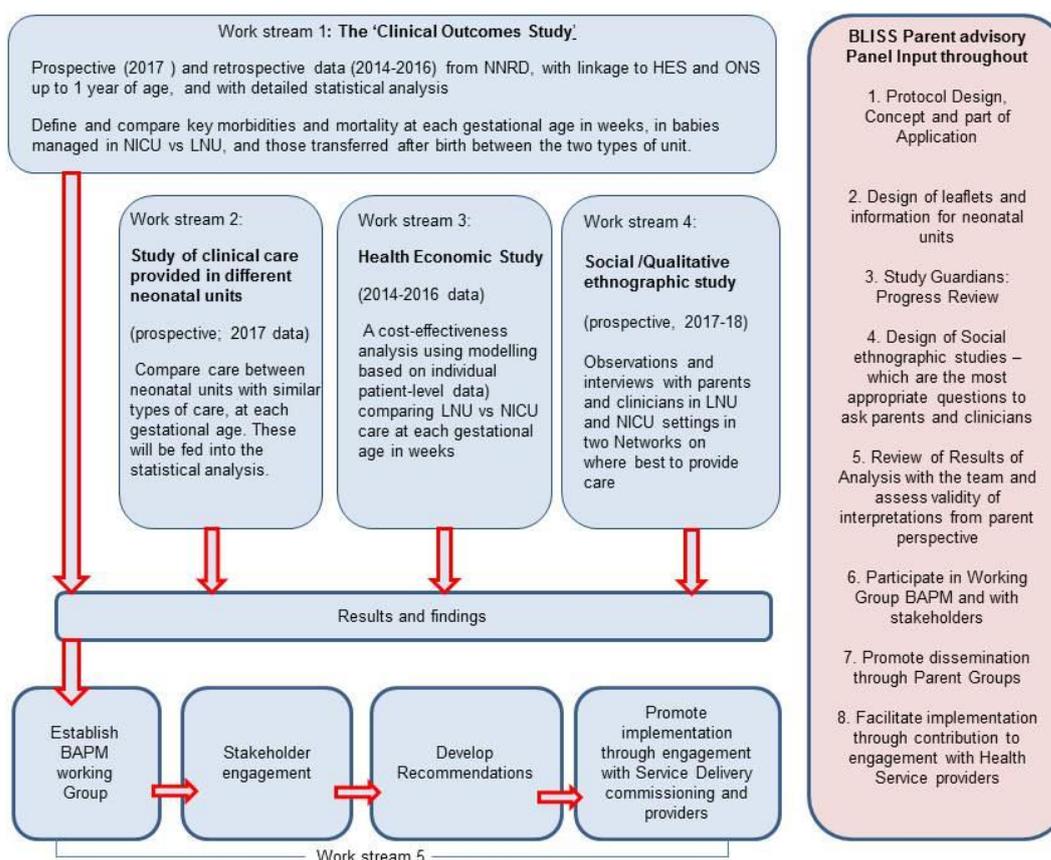


Figure 2: OPTI-Prem Flow Diagram

(HES = Hospital Episode Statistics –to capture morbidities through utilisation of hospital care in the first year of life, and ONS= Office for National Statistics-to capture deaths in the first year of life, after discharge from Neonatal unit care)

Feedback Loop for data: Data from 01/01/2014 to 31/12/2016 will be obtained from the NNRD as 'retrospective data'. Data from 01/01/2017 to 31/12/2017 will be extracted as 'prospective' data. This 'prospective' limb will have been subjected to an additional feedback loop (data returned to neonatal

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units for confirmation of entries) to ensure added robustness to the quality and completeness of data. This will allow development of initial statistical models using retrospective data, to be validated and refined using prospective data. Feedback loop mechanisms were developed by the NDAU as part of data quality assurance methods for the Department of Health commissioned National Neonatal Audit Programme (Figure 3), and will be expanded to include variables for this project. In brief, standard management and checking procedures for data extracted from neonatal Electronic Patient Records and submitted quarterly to the NDAU involve linking patient episodes across hospital transfers, and examination to identify out-of-range, inconsistent, duplicate and missing values. The additional feedback mechanism involves posting all variables to be utilised in specific analyses, including flagging any identified as potentially erroneous, on a specific password protected on-line portal developed and managed by the NDAU, where they may be reviewed by submitting clinical staff. Errors and missing values are corrected on the infant's Electronic Patient Record and subsequently transmitted to the NDAU in their Next Quarterly Action.

Data (Variables listed in Appendix II) will be made available to the research team in 2 tranches: a) at the beginning of the project; January 2017, comprising cleaned data for 2014 to mid 2016, and b) in June 2018, comprising the latter half of 2016, and all 2017 data (which will have been subjected to the feedback loop). At ~6000 admissions per year in England, and assuming there are no neonatal units who opt-out, the study will comprise data on approximately 24 000 neonates between 27-31 weeks gestation.

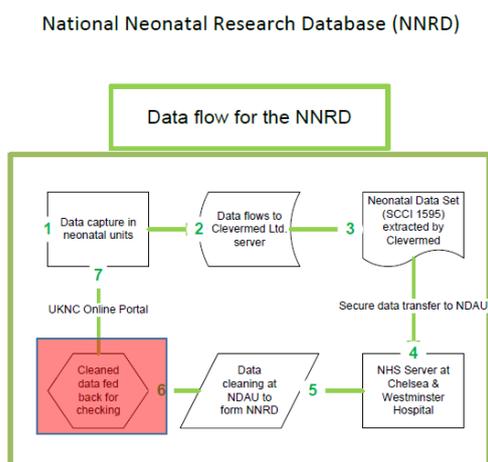


Figure 3: Data Flow for the NNRD showing Feedback loop, for data robustness reassurance

b) Outpatients, up to 1 year (365 days) of chronological age: The National Neonatal Research Database (NNRD) contains clinical information on all babies admitted for specialised care to NHS Neonatal Units, up until the point of discharge from neonatal unit care. To assess outcomes (survival and morbidities) to one year (365 days) of age, NNRD data will be augmented by :

1. Linking to episodes of post-discharge-from-NNU hospitalisation of preterm babies through Hospital Episode Statistics (HES). HES is an administrative database, covering all admissions to NHS hospitals and are available at a charge through the Health and Social Care Information Centre (now NHS Digital).
2. Linking to Office for National Statistics (ONS) dataset, which holds information on location and cause of death, obtained from death registration records.

The NNRD has been successfully linked to HES and used to follow infants discharged from neonatal units up to the age of five years through sequential record linkage. The NNRD has examined data completeness, quality, and the agreement of key variables in the NNRD and HES, and established

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the feasibility of linkage of record linkage using a deterministic approach. They found NNRD to be more complete than HES (babies with missing and implausible birth weights were NNRD 0.1% and 0.2%, and HES 26.4% and 1.5%, respectively; overall agreement between the NNRD and HES for key perinatal variables was >95%). Of 47,345 eligible NNRD records, 93.8% were able to be linked with HES (unpublished data; N Modi 2016).

The NNRD has also been able to create a birth cohort from linked NNRD-HES-ONS records to determine mortality in the early neonatal (0-6 days), late neonatal (7-27 days) and post-neonatal (28-365 days) periods by gestational age, and identify the cause, and risk factors for deaths in the first year across these time periods (unpublished data, N Modi).

Sample size: In 2014, approximately 6,000 babies were born at 27-31 weeks gestational age in England and admitted to neonatal care. Of these babies approximately 48% were born and initially managed in a NICU and 41% were born and initially managed in a LNU, with the remaining babies cared for in a SCBU. Therefore over the four years we anticipate a sample size of approximately 24,000 and of these 21,000 would be born and managed in a NICU or LNU.

In this sample we would expect an in-unit mortality percentage of approximately 5%, giving an over 1,000 deaths in the sample. Assuming 5.0% of babies in the NICUs died before discharge, this anticipated sample size of 21,000 admissions (1,100 deaths in a NICU and 1,000 in a LNU) would give a minimum detectable difference of 2.6% in mortality for the LNUs with at least 80% power at the two-sided 5% significance level in a simple comparison.

The inclusion of over 1,000 deaths in the study is expected to provide sufficient statistical power to investigate the potential predictors of mortality and morbidity.

Statistical Methods: Estimates of differences in mortality and the specified morbidities (these key clinical outcomes are described in Appendix II) between babies cared for in a LNU and NICU will be obtained using Inverse Probability of Censoring Weighted (IPCW)¹⁹ models. This statistical approach will be used to take into account the transfer of infants from one type of unit to another and to reduce any bias which may arise from selective transfers.

Differences in the care provided will be described and compared between babies managed in NICUs and babies managed in LNUs using appropriate generalised linear models: including logistic and log-linear modelling. Generalised linear hurdle models²⁰ will be used where not all babies experience the outcome of interest, e.g. days of respiratory support as some babies will not receive any respiratory support.

To enable a causal interpretation to be inferred on statistically significant associations identified in the analyses, Directed Acyclical Graphs (DAGs)²¹ will be created in order to explicitly specify potential clinical, or demographical, causal pathways. This approach allows identification and statistical control of potential confounders and effect modifiers within a causal framework. These DAGs will be specified a priori using clinical knowledge and existing literature; their plausibility will be further assessed using data from this study. Appropriate methods for modelling continuous predictors will be investigated, including the use of splines and fractional polynomials. A random-effects term for the units will be used to accommodate the hierarchical structure of the data: that is, babies clustered within units. The level of care received by each baby will be included as a fixed-effect indicator variable. Cluster analysis will be undertaken to group similar LNUs, based on the care provided and available facilities identified in Work stream 2, as there is likely to be heterogeneity in the care provided by different LNUs. These clusters will be used to investigate whether any differences in outcomes between NICUs and LNUs are confined to certain types of LNUs.

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Associations will be reported using appropriate summary statistics with 95% confidence intervals. Model checking will be undertaken using appropriate methods, including residuals, DF-betas and, for logistic regression, the c-statistic and Hosmer-Lemeshow test.

Minimising the risk of confounding and reverse causality:

This is an observational study, and the issue being addressed (the optimum location of care) is not amenable to randomisation. For this reason a number of steps to minimise the risks of confounding and reverse causality have been included as expanded on below. A major strength of the project is that the approach is based on a whole population dataset that offers opportunity unparalleled anywhere in the world to address this important question. The dataset is both extremely large, thus offering excellent statistical power, but also contains a large number of socio-demographic and clinical variables which will be employed.

The likely differences in characteristics in babies admitted to the different categories of neonatal units will be accounted for in the analyses using two statistical approaches:

- 1) The use of Inverse Probability of Censoring Weights²² in order to account for movement between categories of neonatal unit, in a similar manner to crossover between treatment groups in a clinical trial. The weights will be estimated using factors known to be associated with neonatal mortality and morbidity. These will include factors identified in a recent systematic review of the prediction of neonatal mortality²³, viz gestational age, birth weight, sex, ethnicity, and antenatal steroid use. These factors have also been identified in another recent review investigating length of stay in neonatal care (unpublished data)²⁴. In addition, other proxy measures of disease severity (including Apgar, CRIB II score) will also be considered for inclusion in the calculation of the modelling weights where these are strongly associated with survival²⁵, particularly long-term survival beyond infancy.
- 2) All potential confounders will be considered for inclusion in the Directed Acyclical Graphs in order to identify potential causal pathways. The development of the DAG will include both clinical and statistical evidence and will allow the estimation of causal effects in the absence of confounding as far as is possible with the available data.

Confirmatory analyses will be undertaken using matched cohorts. The cohorts will comprise babies with similar characteristics identified both clinically and through the use of propensity scores - a method that uses a large number of variables to create matched groups, in effect a form of quasi-randomisation.

Pre-specified sub-group analyses will also be undertaken; these will include singleton/multiple pregnancies; babies that received/did not receive antenatal steroids; and babies that received/did not receive antenatal magnesium sulphate.

Statistical analysis for the post discharge outcomes will be conducted as for the in-unit statistical analyses, with comparisons in outcomes (mortality, hospital service utilisation and ICD10 clinical coding) based on place of care (LNU vs NICU). The principal driver for statistical methods regarding sample size remains the in- unit mortality rates, as we consider this the most near contemporaneous outcome that could drive service change.

Inclusion and Exclusion criteria:

- All babies born at 27-31 weeks of gestation, and admitted into neonatal units, whose records are captured on the National Neonatal Research Database will be included for the study period between 01/01/14 and 31/12/2017.
- Data on babies from neonatal units who elect to opt-out of this project will be excluded.

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- Units will be offered an opt-out option in the preparatory phase, prior to the start of the project in 01/01/2017

Exploratory Work: While the primary objective would be to address differences in outcomes between babies cared for at each gestational age in a NICU vs LNU, we would be exploring the potential of identifying set point at which care can be equitably provided between NICU and LNU. In addition, we would be undertaking exploratory work in identifying the risk factors, (potential explanatory variables- APGAR scores, inotropic agents), not only as adjusting for confounders, but also as Independent variables that define degree of illness warranting NICU vs LNU care.

Work stream 2: Study of clinical care provided in different neonatal units

This will address the secondary objective to identify key differences in care provided in different types of neonatal units, and whether these are associated with gestation-specific differences in outcomes. It is known that variation in clinical practice varies in the management of both extremely preterm³⁹⁻⁴¹ and late preterm babies¹⁸. In this study we will interrogate the NNRD data obtained to explore variation between units in key areas of clinical care for babies of 27-31 weeks gestation. We will use questionnaires and a review of written guidelines in the same key areas from each neonatal unit to explore this further between 01/01/017 and 31/12/2017.

These areas of clinical review will include:

- a) Average medical and nursing staffing levels, and grades;
Policies and practice with respect to
- b) the use of mechanical ventilation and non-invasive respiratory support;
- c) Infection control,
- d) Infant feeding,
- e) Developmental care, and
- f) Discharge and Length of Stay on neonatal units.

Where appropriate and possible, key primary neonatal outcomes (mortality, chronic lung disease, line sepsis, receipt of breast milk on discharge and length of stay in hospital) will be analysed between units with similar practices. If variation is found by interrogating NNRD data, together with collated information on neonatal unit practices, then a further study (outside the scope of this application) would be pursued, to identify possible reasons, and put these to the test of a Randomised Controlled Trial.

Adjusting for heterogeneity within the types of units studied:

Workstream 2 includes a survey of all neonatal units in order to obtain details about their service provision; including capacity, staffing levels and the medical facilities they provide. This information, along with information about the population of babies which are cared for at their unit (but not including the baby's outcome) will be used to undertake a cluster analysis. This analysis will provide groups of neonatal units which are similar to each other in terms of the care that they provide, including volume of care and whether they provide supra-regional services such as ECMO, surgery, therapeutic cooling. The groups of units obtained will then be used to investigate neonatal outcomes to assess the robustness of the results obtained in Work Stream 1 across the potential heterogeneity between units.

Further investigation of this heterogeneity will be undertaken by grouping the units according to each characteristic of care in turn in order to identify the most important characteristics in determining outcome. This means that the analyses will be based not only on designation, but in a series of sensitivity analyses, also on the care actually provided.

Work stream 3: Cost-effectiveness analysis

To address the secondary objective of where it is most cost-effective to provide care, we will compare costs and outcomes associated with care in a LNU compared with that in a NICU. Data extracted from the NNRD will be used to conduct an economic evaluation using individual observational patient-level data comparing the two settings. A UK NHS and societal perspective will be adopted and the primary health outcome measure in the economic analysis will be number of lives saved in each strategy.

A detailed cost-analysis of the neonatal care received by preterm babies in a LNU or NICU will be carried out. The main healthcare resource use categories will include time spent in the neonatal unit by level of care, non-routine investigations, surgical procedures, transfers and post-mortem costs. Unit cost for neonatal care received will be extracted as a *per diem* cost for the level of care (intensive, high dependency, special care, transitional care) from NHS Reference costs 2014-2015. Non-routine investigations not included in the NHS Reference *per diem* costs will be valued using data from secondary sources. Procedure costs will be calculated allocating surgical procedures to Healthcare Resource Groups and applying national tariffs. Transfer costs will be extracted from NHS Reference costs 2014-2015. Post-mortem unit costs will be extracted from secondary sources.

The statistical analysis will aim to identify any differences in the number of lives saved and costs between neonatal care settings. We will employ matching methods to address selection bias in the analysis²⁶. We will also follow current guidance on conduct of economic evaluations using observational data to assess the main assumptions for addressing selection bias in the statistical models implemented²⁷. Net-monetary benefits (NMB) will be used to present the results of the cost-effectiveness of LNU versus NICU. Parametric and non-parametric bootstrap methods will be employed to evaluate any uncertainty around differences in lives saved, costs and NMB²⁸. Lives saved, costs and NMB will be presented for different strategies of LNU and NICU neonatal care and by gestational age in weeks. The main comparison in the economic analysis will be between babies managed only in LNUs or NICUs but the impact of transfers between the two settings on the cost-effectiveness will also be assessed.

With linkage of data from HES and ONS to the NNRD the time horizon of the economic evaluation will be up to 1 year of age. A comprehensive cost-analysis using the methodology above will be conducted to identify whether patterns of service use of hospital admissions, outpatient visits and A&E differs across neonatal strategies at 1 year-follow-up. We will follow current guidance for methods of technology appraisal to present and report the results of the economic analysis²⁶.

Work stream 4: Social ethnographic study with parents and clinicians

This will address the secondary objectives of exploring parents' and clinicians' perspectives regarding place of care, and whether these can be used to guide decision making on place of care

Observations and interviews will be used to explore the following questions:

- What factors do parents think should guide decision making about where babies cared for, and how does this happen in practice?
- What are clinicians' perspectives and practices around decision making about place of care?

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- What are the impacts on parents and families of this decision, and any subsequent change in care location?
- How can parents' best be supported at this time?

Target population: We will recruit up to 40 cases across two neonatal networks – 20 will be 'real-time' cases in which the baby is currently receiving neonatal care, and 20 will be 'retrospective' in which the baby has since been discharged.

Inclusion criteria and recruitment: Participants (parents and clinicians) who are willing and able to give informed consent will be included. Participation will be voluntary and it will be made clear to parents in particular that declining will not compromise the care they or their babies receive. Written information will be developed for both parents and clinicians invited to participate in the ethnographic study and informed consent for participation obtained. Where parents are unable to communicate in English, we will explore use of translation services.

Data collection: For 'real-time' cases we will conduct periods of observation within neonatal units, observe discussions between clinicians and parents, and carry out interviews with both groups. For real-time cases, clinicians will introduce the study at their first meeting with parents, and provide written information. We will observe all possible discussions that take place between parents and clinicians and keep in touch with parents at regular intervals, although flexibility will be needed. An experienced and sensitive qualitative researcher will carry out the observations, and will make decisions about when it is appropriate to withdraw temporarily. Alongside these observations, we will also seek to conduct interviews with parents and clinicians.

For the 'retrospective' cases we will interview parents about their experiences of having had a baby receive neonatal care within the past 12 months. To recruit these 'retrospective' cases, clinicians will be asked to identify eligible parents and send them information about the study. Those willing to participate will be asked to contact the research team directly and an interview will be arranged.

We will seek to recruit a diverse range of cases to include:

- Parents with babies born at different gestations between 27-31 weeks.
- Parents for whom this is a first or subsequent pregnancy.
- Parents of babies on different care pathways (e.g. moving from LNU to NICU and vice versa).

Within this 'retrospective' work we will also seek to interview clinicians from within the two Neonatal Networks who we have not observed or interviewed during the course of the 'real time' work.

For both parts of this work ('real time' and 'retrospective') interview topic guides will be developed and piloted through discussions with the project team and Parent Advisory Panel. For parent interviews we will aim to interview both parents together but will be flexible according to individual families' preferences and circumstances. Interviews will be carried out by an expert qualitative interviewer, and will last up to an hour. Interviews will be audio-recorded and transcribed verbatim. Observations will be guided by an observation framework, again developed through discussions with the project team and PPI representatives. The observer will take written notes unobtrusively and will then de-brief these either alone or with another member of the team. These de-brief sessions will be audio recorded and transcribed.

Data analysis: The qualitative data will be analysed using the constant comparative method²⁹ assisted by NVivo software. A coding scheme developed through detailed engagement with the data will be used to process the dataset systematically by assigning each section of text to a category, according to the category specifications. PPI representatives will be invited to comment on the face validity of the analysis of qualitative data.

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Conducting research in sensitive settings: While this is undoubtedly a sensitive area, we do have previous experience of successfully completing qualitative work of this type in highly-charged settings, e.g. intensive care units and fetal medicine. We are confident that this experience, together with the guidance and support available through our PPI representatives, makes this element of the project feasible. We are aware that some babies, particularly those born very early, may not survive, so working with parents in these cases will need to be handled very sensitively.

Accounting for diversity, ethnicity and adequate representation of at communities at risk of preterm births: We will attempt to recruit a diverse sample of parents with babies born at different gestations between 27-31 weeks, parents for whom this is a first or subsequent pregnancy, and parents of babies on different care pathways (e.g. moving from LNU to NICU and vice versa). We will do all we can to ensure diversity of participants in relation to maternal age, ethnicity, socio-economic status and educational background. We will also include clinicians of different ethnic backgrounds, ages and sexes. We will be limited to some extent by the clinicians and participants available to us in each of the two recruitment elements (those who have a baby on the neonatal unit at the time for the 'real time' element and those whose baby has received care on the unit in the last 12 months for the retrospective element).

In the discussions with the parent panel, parent information leaflets, and their input into the project as a whole, the research team will ensure consideration for diversity, ethnicity and adequate representation of communities at risk of preterm births is given.

Translational aspects: Translation for parent leaflets and interviews to accommodate the three commonest languages for which translation is likely to be needed viz Arabic, Hindi and Polish will be addressed.

Work stream 5: Collaboration with the BAPM to establish framework documents and recommendations on place of care

Following analysis of data and conclusions the final work stream (Work Stream 5), will be set up. This is anticipated to be done in the final 6 months of the study project, but continue beyond the end of the study funding period. The details of these are discussed in the 'Dissemination and Output' below.

Briefly, the project team anticipates collaboration with BAPM to establish a working group. This will include the Parent Advisory Panel. It will include engagement of relevant stakeholders and other parent support groups, with a purpose to establish a framework document and design recommendations for place of care for babies born at each gestational age between 27-31 weeks, based on the evidence from this NIHR study.

Recommendations from this working group will be published, presented at local and international meetings, and made available to health service delivery planners in England. This will impact on delivery of neonatal care as below.

DISSEMINATION AND PROJECTED OUTPUTS

DISSEMINATION

Main knowledge products from the research: The findings from this study will inform where best to manage babies (i.e in a LNU or NICU), at each week of gestational age, between 27-31 weeks gestation. It will have considered the clinical outcomes, and where these are in equilibrium between LNU and NICU, the most cost effective place of care, as well as parent and clinician perspectives. Major outputs will be:

a) Presentation and publication of research findings

We will present the study results at national and international perinatal, neonatal and paediatric conferences, and submit them for publication in appropriate high quality, peer-reviewed journals to disseminate important findings to relevant professionals and professional organisations.

b) Development of recommendations for care of the neonate born at 27-31 weeks of gestation

Working together with BAPM and BLISS, we will form a working group to define position statements and recommendations regarding the most appropriate place of care for babies born at this gestation in England. These organisations have agreed to support the findings of the study. BAPM provides advice to the government and professional bodies on delivery of perinatal care, and BLISS, on improving care for preterm babies and their families. We envisage that this working group will be led by investigators from our study and will incorporate nursing and medical professionals with relevant expertise (following a national call by BAPM), representatives from the project's parent advisory panel and additional parent representatives.

c) Consultation with health care professionals and other stakeholders

Framework documents and recommendations will be processed through the BAPM. This includes consultation with members and stakeholders (managerial stakeholders including Commissioners, Networks, Trusts; Governmental/Regulatory stakeholders including the Department of Health, Public Health England, National Commissioning Board, Care Quality Commission, National Institute for Health Care Excellence; and educational stakeholders including Royal Colleges and professional societies).

d) Publication and dissemination of recommendations

It is anticipated that recommendations will be published via BAPM and RCPCH. Further dissemination will occur via the neonatal CRG to inform evidence based commissioning of neonatal services in the future and BLISS to inform written information for parents, parent counselling and support services.

EXPECTED IMPACT/OUTPUT

Our work will lead to recommendations which will have an impact on the following categories:

1. Impact on babies

Reduction in morbidity and mortality: By defining a care pathway for babies at each week of gestation from 27 to 31 weeks, we will be able to develop clear guidelines to streamline delivery of care for a large number of babies in England. Individual babies will therefore benefit from receiving the most appropriate care, from the most appropriately trained staff in the centre most appropriately equipped to meet their needs. Greater standardisation of care is likely to result, which is known to have positive effects on morbidity at a population level over time; this effect would be expected for important

neonatal morbidities such as infection and chronic lung disease. This is likely to be generalizable to similar settings in other developed countries.

2. Impact on mothers

Although our primary aim is to determine the most appropriate place of postnatal care for preterm babies, we anticipate a secondary impact on the care of mothers with threatened preterm labour or pregnancy complications requiring early delivery. If the most appropriate pathway of care can be defined based on best outcomes for babies, then it will be possible, when safe to do so, for a mother to be directed or transferred to the most appropriate maternity centre for delivery of her preterm baby. The effect of this will be to reduce risks and costs associated with postnatal transfer of the baby.

3. Impact on families

a) For parents, our work will provide a clearer understanding of what to expect if their baby is born early, and in particular where their baby is likely to be cared for. This will reduce stress and anxiety associated with preterm birth *per se* and the added effects of anticipated transfer of the baby for care away from home.

b) It is likely that our work will lead to changes in the pattern of postnatal transfer of babies between neonatal units. For some parents, this will mean a greater likelihood of care nearer home with reduced anxiety and costs. For those where transfer is necessary, we will be able to develop strategies to better support parents based on outcomes from our qualitative work.

c) Identifying the likely personal and family costs of having a preterm baby at a specific gestation will allow families to appropriately manage their finances, either through their own resources or by seeking support from other agencies.

d) Working in partnership with parents in this study to facilitate decision making will allow parents to feel included, and to understand and accept the care pathways most appropriate for their baby.

4. Impact on neonatal clinical teams

a) Evidence-based standardisation, in terms of pathways of care for these babies will mean that units become more experienced and skilled in delivering appropriate care to a selected cohort of babies.

b) Reduced mortality and morbidity are useful indicators of improvements in neonatal unit performance. Targets already exist within the National Neonatal Audit Programme (NNAP), National mortality data analysis (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE) and NDAU network mortality reporting. Improved performance within a neonatal unit will boost staff morale and pump prime for continued excellence in clinical care.

5. Impact on other health care providers

a) Based on recommendations from the study we will be able to guide professionals in obstetrics, primary care, emergency care and ambulance services on where best to direct, if safe to do so, a mother at a specific gestation in preterm labour, so that her baby is born at a hospital with the most appropriate facilities for neonatal care.

b) Redirecting a mother to the correct maternity facility will be cost effective, as opposed to transporting a preterm baby after birth to the most appropriate neonatal unit.

6. Impact on neonatal service provision

A defined care pathway for babies born at 27-31 weeks will help to ease current pressures experienced by both NICUs and LNUs in providing appropriate care for these babies. A likely impact will be less 'blocking' of NICU cots by preterm babies who can safely and effectively be managed in a LNU, thus freeing up NICU cot space for a neonate requiring higher intensity care. Similarly, 'blocking' of intensive care cots in a LNU, if the sicker more immature preterm baby is transferred out in or ex utero will be avoided.

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7. Impact on Commissioning: Service and economic implications for the NHS

This study may reveal that changes in the configuration of neonatal services are required to obtain optimum outcomes for babies, families and the NHS. This could have implications for cot capacity, unit designation and bed utilisation in Newborn Networks (eg. more beds in NICU vs LNU or vice versa). Our data will support working towards a situation where care for the sickest infants is consistently provided by units most able to deliver highly specialised care and care for the less ill and more mature infants is provided in the most cost effective manner by units best equipped for this.

Appropriate re-direction of care will allow Networks and Commissioning teams the opportunity to more accurately predict future cot utilization assumptions, which will better inform commissioning of neonatal cots, staff and other resources.

The benefit of having three categories of neonatal units in England (NICU, LNU and SCBU) is currently under discussion. This research will provide information on whether a LNU facility is of benefit for babies born between 27 and 31 weeks gestation. It will contribute to a body of work that could lead to simplification of, or other changes in the current categorisation of neonatal care.

Any recommendations for change resulting from our work will therefore be evidence-based and considered from both the health benefit and cost benefit viewpoints, whilst attending also to the needs of families. Implementation of any changes will require close engagement at a local level with commissioners, neonatal care providers, managers and the general public. Should reconfiguration at a national level appear to be warranted, liaison with the BAPM will facilitate discussions and negotiations at the highest level for the management of change.

8. Impact on the NHS and society

This research has the potential to significantly reduce the costs associated with preterm birth. Although the small number of babies born at 23-26 weeks are at highest risk of serious neonatal morbidity and long-term adverse outcomes, birth at 27-31 weeks of gestation nevertheless carries a substantial risk of later chronic respiratory illness, neurological and cognitive impairment, developmental delay, behavioural problems and educational difficulties. For the NHS, these problems represent a significant healthcare burden that, because of larger numbers of births in this gestational age range and greater survival, probably outweighs that of the group born at 23-26 weeks. Effects of preterm birth are seen throughout the whole lifespan³⁰ and influence social integration, education and employment opportunities with attendant societal consequences and financial costs¹¹. We now know that long-term effects of preterm birth can be modified in the most immature babies by delivering care in the most appropriate environment. It is likely that this will also be true for this slightly more mature group and that improvements in the delivery of neonatal care will have long-lasting effects that will reduce the burden of health care and societal costs in a large preterm population.

PLAN OF INVESTIGATION/TIME LINE (36 months)

- *Months -3 to -6:* Approval for use of the NNRD will require a proportionate (expedited) Research Ethics review and R&D approval from the Chelsea and Westminster Trust; this will be done as soon as notification of success of grant application is sent, and will precede the start of the project.
- *Months -3 to 0:* Neonatal units will be informed of the project, via a prepared electronic leaflet detailing a synopsis of the project, and will have the option to opt out of the research.
- *Months -1:* The parent advisory panel will receive one day of training in advance of the start of the project, including familiarisation with the study protocol, meeting the team, an overview of parent

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involvement in public research (INVOLVE) and discussion about anticipated requirements of the panel during the course of the research.

- *Months 0-36:* A research assistant/fellow will be recruited prior to the start of the project, to be employed and commence work at the start of the research
- *Months 1 and 18:* Data issue to the project team will be made from NNRD via NDAU at two time points a) at the beginning of the study period for 2014/2015 and 2016 cleaned data, b) in June 2018, for remaining cleaned 2016 data, and all 2017 cleaned data.
- *Months 1-36:* Preliminary analysis will be undertaken using 2014/15, the 2016 data, with final analysis after including 2017 data. A statistician will be employed from 01/01/2017 to 31/12/2019.
- *Months 1-12:* The Unit questionnaire study will run from 01/01/2017 to 31/12/2017. The information obtained will be collated before transfer to the data analysis team to assess impact on types of care on clinical outcomes.
- *Months 0-36:* The Parent Advisory Panel will assist in developing documentation and preparatory questions for the ethnographic studies, and will have 6 monthly reviews with the research team as 'Project Guardians'. Members will be consulted to review interpretation of final results and begin the process of engagement with working groups and stakeholders.
- *Months 0-36:* The cost-effectiveness study will run throughout the duration of the project, and will filter relevant data from the 2014-2017 datasets
- *Months 0-18:* The ethnographic work will be undertaken in the first 18 months of the study
- *Months 30-36:* Preparations for publications will begin; a BAPM working group to develop recommendations from the study findings, with parent and stakeholder engagement will be set up.
- *Months 6-30:* A Senior data analyst with link, and clean ONS and HES data to the NNRD, for analysis by Health economic and statistical teams.
- A feedback report will be sent to the NIHR 6 monthly.

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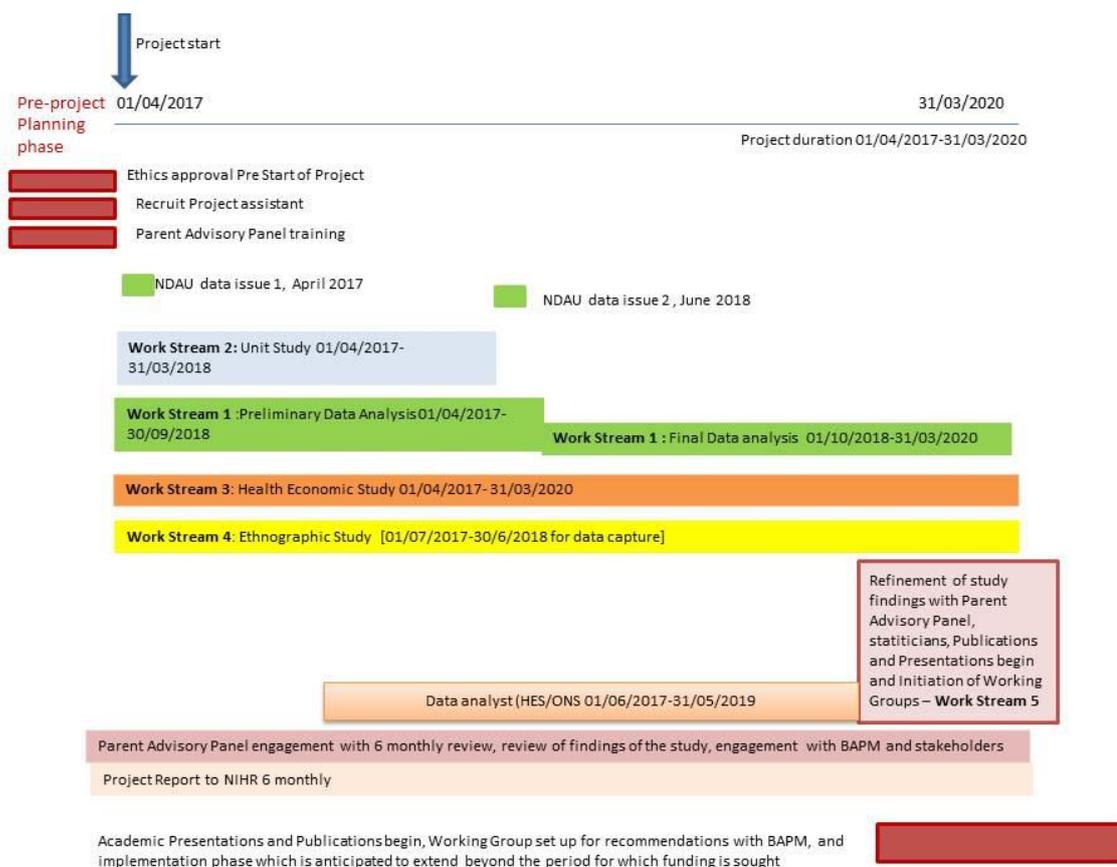


Figure 4: OPTI-Prem Time Line

PROJECT MANAGEMENT

The chief applicant TP will be the overall manager of this project and will be supported by EB, and NM. This will include

- Monthly meetings to review progress of project, either face to face or by telephone;
- Guidance on oversight of the four streams of the project
- Assistance with interpretation of data following analysis
- Guidance with the preparation of study reports and manuscripts
- Support with working group discussions through BAPM, to develop recommendations
- Support in presentation of results and recommendations to the relevant bodies

TP will employ a Research Assistant/Fellow for administration of this study. This will include

- a) Co-ordinating Parent Advisory Panel meetings
- b) Co-ordinating investigator meetings
- c) Co-ordination and conduct of the questionnaire based study
- d) Data entry for the questionnaire based study
- e) Communication with participating units to ensure smooth running of the study

The day to day Study Management will be the responsibility of TP, together with her research assistant, and supported by EB and NM, her mentors.

The Study Steering Group will comprise all of the co- applicants and the Parent Advisory Panel Lead.

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TP will co-ordinate Parent Advisory Panel meetings. RWT will sponsor the study, and the Research and Development Team will be chiefly responsible for co-ordinating the budget. TP, guided by NM, will design the information leaflet for neonatal units to explain the project. TP and EB will design the unit questionnaire, collate and interpret the data captured regarding clinical care provided in different units and submit this data to the statisticians to evaluate key clinical outcome variables against different groupings of units. TP, with support from NM, EB, NA, ED will prepare the protocol for Research Ethics Approval (National Research Ethics Committee; NREC), in line with 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) principles³¹.

BM will supervise SS in the statistical input for this project. BM and SS will recruit a designated statistician to undertake statistical analysis for the project. This statistician will be based at the University of Leicester, but will travel between NDAU and RWHT sites as needed to support cohesive flow of information. TP will engage with the statisticians weekly for telephone discussions, email communications and assessment of progression with study analysis.

TP will be responsible for submission of 6 monthly interim reports to the NIHR on progress with study timetable and milestones achieved.

TP will be responsible for monthly reviews with the health economic and social science elements of the project. TP, with EB will engage closely with epidemiologist ED.

NA will employ and supervise an appropriately trained and experienced research associate to conduct the ethnographic component of the study.

NA, her research associate and TP with her study assistant/fellow will meet with Parent Advisory Panel members to define questions to be considered in the ethnographic component of the study.

NA will be responsible for conduct of the ethnographic study. NA/research associate will liaise closely with TP regarding updates on progress. NA will contribute to group discussions in the analysis phase of the study and contribute to the working group discussions on recommendations.

ORA will be responsible for the cost-effectiveness analysis study and will supervise a health economist who will conduct this work. ORA will request data variables from BM/SS for this analysis. ORA and TP will have regular meetings to assess progress of the project and to ensure cohesive flow of project. ORA will contribute to interpretation and recommendations based on the results of the study.

The data analyst employed for the HES and ONS data linkage and cleaning will be supervised by NM and ORA.

APPROVAL BY ETHICS COMMITTEE

1. Ethical approval for use of the NNRD for this research will require a proportionate (expedited) review through NHS Research Ethics Committee (NREC), for Work stream 1 and full review for Work stream 4 (see point 4 below). This will be requested should this project be funded through NIHR. This will precede the start of the project. It is anticipated that a decision on this project should be available mid 2016; allowing 6 months for ethical approvals to be addressed.

2. Further R&D approval from Chelsea and Westminster Hospital will be sought; this will take approximately 3 months.

3. For NNRD Data: National Research Ethics Service (ref 10/H0803/151) and the Ethics & Confidentiality Committee of the National Information Governance Board (ref ECC-05(f)/2010) have approved utility of the database, and the NNRD is open to use by other investigators. For study purposes, unidentifiable anonymous data will be obtained from the National Neonatal Research Database and transferred to the Wolfson Institute of Preventive Medicine (Queen Mary University of London) using the NHS Net.

Data from all neonatal units in England will be used. Individual units will be sent a leaflet informing them of the project, with opportunity to engage for the unit, or to opt-out of participation.

4. Ethnographic work (Work stream 4): The ethnographic work will require ethical approval from an NHS Research Ethics Committee and R&D approval from the trusts involved. We will ensure

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applications for these necessary approvals are submitted in good time and are of a sufficiently high quality to expedite timely approval. We are very experienced in successfully securing the ethics and governance approvals required to conduct qualitative research in healthcare settings, including those which are sensitive. Written information materials will be developed for both parents and clinicians invited to participate in the ethnographic study and informed consent for participation obtained.

PARENT AND PUBLIC INVOLVEMENT IN THIS PROJECT

Contribution to project development: In preparing this application, a BLISS volunteer focus group discussion was held with parents of preterm babies cared for in the Black Country. This sought to explore parental perceptions on care and movement of their babies between types of neonatal units and to evaluate how best to engage parents in a project aiming to refine neonatal service delivery. Prior to having had a preterm baby, parents reported that they did not have any significant understanding of these types of neonatal units, or how and why this could have relevance to their babies' outcomes: 'I originally thought that all hospitals in the NHS were the same'; 'I did not know that different hospitals had different abilities to care for babies'. They clearly expressed that the most important criterion, having had a preterm baby, was that their baby was managed in a unit that was able to provide the most appropriate care for their baby, and which afforded the best possible outcomes for their baby and families. They did not regard cost to themselves as an important factor in determining appropriateness of care provided for their baby, but noted that being away from the close family/home environment was difficult, more costly and that greater support was needed for parents who had to move to be close to their baby. They supported research into defining where best very preterm babies ought to be delivered and managed, and how best to support families whose babies were being cared for elsewhere. Parents felt that research based on place of birth was valid' with clinical outcome being their main concern. They noted the importance of considering parent perspectives in developing strategies on where babies should be cared for, and recommended broadening recruitment for parents nationally, through a national BLISS advert. 42 parents responded to this national advert, and 10 were selected to form a parent advisory panel. The panel members include those with experience of preterm births at 27-31 weeks gestation, transfers between hospitals and preterm death.

Further Parent Advisory Panel input: The panel will receive a day of training to include reviewing the principles of public engagement in clinical research (INVOLVE³²), reviewing the project protocol, and guidance for preparing parent information leaflets. This panel will contribute to study documentation and will inform the ethnographic component of the study regarding the most appropriate aspects to assess when undertaking the qualitative study. They will act as 'Guardians' of the project, with 6 monthly reviews with the chief investigator to assess progress. They will review the findings of the study and assess whether the conclusions drawn and interpretation of results is appropriate. They will contribute to working group discussions in establishing national recommendations for place of birth for these babies, and dissemination of parent information. The parent co-applicant will chair the advisory panel, and be part of the steering group for this project. The steering group for this project will be made up of the co-applicants.

RELEVANT EXPERTISE

This is a cohesive team of clinicians and researchers from major centres of excellence for neonatology in the UK. *T Pillay* (TP) is an experienced neonatologist and lead clinician with expertise in developing national clinical recommendations (NICE, BAPM and NCC) and in leading multinational

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projects, grant applications and publications. She will be responsible for co-ordination of all aspects and organisation and effecting output from this study.

E Boyle, neonatologist (EB), *E Draper*, paediatric and perinatal epidemiologist (ED), *B Manktelow* (BM) and *S Seaton* (SS), statisticians, work within the TIMMS (The Infant Mortality and Morbidity studies) Research Group in the Department of Health Sciences at Leicester University. They have long-standing collaborations on multiple perinatal epidemiological studies including The Neonatal Survey, the NIHR funded Late And Moderately preterm Birth Studies (LAMBS and LAMBS-2), the EPICure studies of <27 week infants and EU-funded EPICE (Effective Perinatal Care in Europe) project. *N Armstrong*, medical sociologist also works within the same department and was a co-investigator in the LAMBS-2 study, providing qualitative input.

O Rivero-Arias (ORA) is the Senior Health Economist in the National Perinatal Epidemiology Unit (NPEU) in Oxford. There is a long history of research collaboration between Leicester and Oxford with previous (EB) and ongoing (EB, ORA) collaborative projects on long-term effects of gestational age at birth. *N Modi* (NM), based at Imperial College, is a senior neonatologist, the lead for NDAU and NNRD, and Chair of the Royal College of Paediatrics and Child Health.. There are well established links and channels of communication between Leicester, NDAU and the NPEU. BM and SS have collaborated with NM and the NDAU in analysis of data from the NNRD and both have considerable experience in handling this and other large datasets.

TP will lead this research, with support from EB and NM. Her expertise in developing national guidelines will be key to translating the research findings into clinical practice.

EB has a particular interest in perinatal epidemiology and outcomes of preterm birth. She led the LAMBS Studies on outcomes of infants born at 32-36 weeks of gestation and will bring this expertise to this research, which considers the outcomes of a similarly heterogeneous group of babies. She will be the principal mentor for TP in this project.

BM and SS are experienced statisticians, whose principal expertise lies in analysing large epidemiological datasets focused on outcomes following preterm birth. BM will provide mentorship for SS and they will undertake statistical analyses and will supervise a research assistant (Grade 7) in this project. NA will lead the ethnographic study. She has expertise in qualitatively exploring experiences, access to and organisation of, quality and safety in healthcare. She will supervise a suitably experienced qualitative researcher (Grade 7) employed for this project.

ED brings extensive expertise in perinatal epidemiology which will contribute to the design and execution of the study and appropriate analysis and interpretation of the findings.

ORA is a health economist with fifteen years' experience in conducting economic evaluations using patient-level data and economic models. He will lead the health economic evaluation and will supervise the health economist employed through the funding for this project.

NM will facilitate access to NNRD data via NDAU and will advise on data completeness quality and interpretation. As President of the RCPCH, NM has substantial knowledge of the configuration of neonatal and paediatric services and extensive experience in providing advice and guidance on issues in neonatal care at a high level. She will provide additional support for TP.

Michelle Greenaway is the parent of a preterm infant and co-applicant, overseeing parent assistance with interpretation, review and contribution to national working group.

APPENDIX I NNRD DATA ROBUSTNESS AND DATA COMPLETION

There are four levels of reassurance for this study. The outcome variables selected are either long standing National Neonatal Audit Programme (NNAP items and highlighted with * in Appendix II), which have been under scrutiny since 2009, BAPM care level items (used for payments), or diagnostic items (details appear in the discharge letter). These parameters incentivise neonatal teams to ensure accurate and complete entry of data.

a) For NNAP items (asterisked in Appendix II) there exists a feedback loop operational to ensure data completeness, whereby units are offered the opportunity to address deficiencies in their dataset before analysis by NDAU for NNAP items.

b) For the remaining items there is overall good data completion. In 2014 NDAU reported⁶ 100% completion of data for gestation, birth weight, location of care, respiratory support, 97% completion for intended place of booking, 95% completion for enteral feeds, 78% for maternal ethnicity. Care level days as defined by BAPM were recorded in 99.9% of care days for neonatal units in England.

Figure 1a Changes in data completeness for key episodic variables by final neonatal discharge year for infants discharged between 1st January 2007 - 31st December 2014

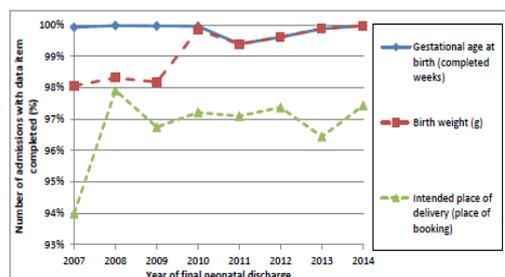


Figure 1b Changes in data completeness for key daily data variables by final neonatal discharge year for infants discharged between 1st January 2007 - 31st December 2014

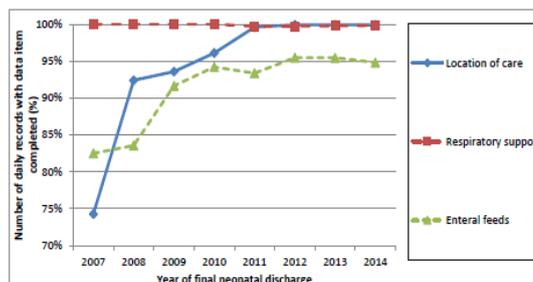


Figure 5: NDAU 2014 Report: Data Completeness⁷

- c) Unpublished data from the NNRD (N Modi, Personal communication and submitted) reveal a high degree of correlation between data captured in electronic patient records from NNRD against a national, NIHR funded trial in the UK (Probiotics in Preterm Infants). While there were deficiencies in some patient outcomes (eg medical treatment for patent ductus arteriosus, we will not be using these variables in our study and discordancy rates were low for most patient characteristics, process measures and outcomes (>85% specificity for all outcomes) that we will utilise in this study
- d) This study will capture data from 01/01/2014-31/12/2017. For 01/01/2017-31/12/2017, robustness of the dataset used will be validated using a feedback loop, already in place for the NNAP. Neonatal units will be offered the opportunity to review and update data over a 3 month period of time before analysis, to ensure most accurate and complete entries. This will be undertaken on a quarterly basis, at the same time as the NNAP variables are fed back to individual units to check. To facilitate compliance, a research assistant/fellow, together with the chief investigators (EB and TP) will be actively engaged in contacting neonatal units, to re-inforce compliance for the project.

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APPENDIX II DATA VARIABLES FOR OPTI-Prem PROJECT

Outcome measure	Variable	Definition	Clinical Outcomes Study	Health Economic (HE) study	Socio-ethnographic (SE) study
Key Clinical Outcomes	Survival*	Survival to discharge from neonatal care (i.e discharge from the neonatal unit)	√	√	√
	BPD/chronic lung disease*	Bronchopulmonary dysplasia; Oxygen dependant at 36 weeks corrected gestation	√		
	ROP requiring laser	Retinopathy of prematurity requiring laser treatment	√	√	√
	Neurological outcomes at discharge	Worst cranial ultrasound abnormalities a) Haemorrhagic parenchymal infarct b)periventricular leucomalacia c) porencephalic cysts d) hydrocephalus (ventricular index >4mm above 97 th C)	√		
	Length of Stay	Length of stay in hospital/s until discharge from neonatal care	√	√	√
	Breast milk on discharge*	Receiving breast milk feeds through any route, on discharge	√		√
Potential Explanatory Variables	Temperature*	Temperature on first admission to neonatal unit	√		
	Antenatal steroids*	Mother receives antenatal steroids	√		
	Surgery*	Any surgery including for NEC, perforated GIT, PDA. Excluding Laser treatment	√	√	√
	NEC	Suspected or confirmed NEC	√	√	√
	Days of TPN	No. of days requiring TPN	√	√	
	Respiratory support	Ventilation, non-invasive ventilation, oxygen (and duration for all)	√		
	Apgar Score	Apgar score at 5 minutes of life	√		
	Multiple pregnancy Inotropes needed	Yes/No, during course of NNU stay	√ √		√
Other Health economic measures (not in HE Column)	Surfactant Replacement	Yes/No		√	
	Nitric oxide	Yes/No		√	
	Blood transfusion	Yes/No and number		√	
	Home oxygen	Discharged home on oxygen		√	
	Chest drain	Insertion of intercostal chest drain		√	
Demo-graphic material	Mother				
	Place of booking	Where mother received her first antenatal care	√		√
	Mother's age		√		√
	Mother's ethnicity		√		√
	Previous pregnancy	Yes/No and number	√		√
	Mode of delivery	Vaginal, caesarean, instrumental	√		√
	Baby				
	Place of birth*	Where baby was born	√		√
	Gestation *	Gestational age in weeks at birth	√		
	Weight*	Weight at birth	√		
	Sex*		√		
	Ex utero transfer	Transferred after birth for care in another unit	√	√	√
Discharge weight		√		√	
Discharge gestation		√		√	

* = items already on feedback loop with NDAU

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Post discharge from NNU outcomes up to 1 year

Outcome measure	Variable	Definition	Clinical Outcomes Study	Health Economic (HE) study	Socio-ethnographic (SE) study
Key Clinical Outcomes	Mortality after discharge from neonatal unit, up to 1 year of age, and cause of death	Deaths recorded on ONS data linked to NNRD	√	√	
	Number of admissions to hospital, up to 1 year of age	After discharge from NNU	√	√	
	ICD10 code for admissions to hospital	Reasons for admission	√	√	
	Number of visits to Accident and emergency up to one year of age	No. of visits and reason for visit	√	√	