

Optimising newborn nutrition during therapeutic hypothermia: an observational study using routinely collected data

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This protocol describes a study entitled “Optimising newborn nutrition during therapeutic hypothermia: an observational study using routinely collected data” 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 NHS Research Governance Framework for Health and Social Care (2nd edition). 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

BPD	Bronchopulmonary dysplasia
EPR	Electronic Patient Record
HIE	Hypoxic Ischaemic Encephalopathy
HQIP	Healthcare Quality Improvement Partnership
IV	Intravenous
LNU	Local Neonatal Unit
IVH	Intraventricular haemorrhage
MRC	Medical Research Council
NDAU	Neonatal Data Analysis Unit
NDS	Neonatal Data Set
NEC	Necrotising Enterocolitis
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health Research
NNRD	National Neonatal Research Database
PN	Parenteral Nutrition
PVH	Periventricular haemorrhage
ROP	Retinopathy of prematurity
SCBU	Special Care Baby Unit
UK	United Kingdom
UKNC	United Kingdom Neonatal Collaborative

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STUDY SUMMARY

- TITLE** Optimising newborn nutrition during therapeutic hypothermia: an observational study using routinely collected data
- DESIGN** Register-based retrospective epidemiological study using propensity score matching
- AIMS** to determine the optimum enteral and parenteral nutrition strategy for newborns with Hypoxic Ischaemic Encephalopathy (HIE) during and after therapeutic hypothermia
- OUTCOME MEASURES** Primary: necrotising enterocolitis and blood stream infection
Secondary: Survival; length of stay; breastfeeding at discharge; hypoglycaemia; time to full enteral feeds; growth
- POPULATION** Infants born in England, Wales and Scotland at greater than or equal to 36 gestational weeks
- ELIGIBILITY** All infants who received therapeutic hypothermia for 72 hours or who died during therapeutic hypothermia, and who are registered in the National Neonatal Research Database (NNRD).
- DURATION** Retrospective, non-identifiable data held in a pre-existing research database (the NNRD) on infants born between 1st January 2008 and 31st December 2016 will be used.

KEYWORDS

Hypothermia, induced; neonatal encephalopathy, parenteral nutrition, breast milk, matching, NNRD

PLAIN ENGLISH SUMMARY

Every year about 1200 babies in England, Wales and Scotland suffer from a lack of oxygen around birth which can lead to long-term brain injury or death. This is called Hypoxic Ischaemic Encephalopathy (HIE). Research has shown that cooling babies with HIE by a few degrees for the first 3 days protects the brain; all babies with moderate or severe HIE in the UK are treated with therapeutic hypothermia (cooling).

Doctors do not know how best to care for babies while they are cooled. A key question is “how to provide nutrition to babies during cooling”. There are two main parts to this question, milk feeds (“enteral” nutrition) and intravenous nutrition (“parenteral” nutrition). We don’t know how best to provide either milk or intravenous nutrition to cooled babies.

- MILK FEEDS: Some neonatal units in the UK carefully feed babies (usually with maternal breast milk) while they are cooled. This avoids intravenous lines and is believed to help them feed and go home earlier. Other neonatal units do not feed cooled babies because they worry about a condition called necrotising enterocolitis (a devastating and often fatal disease) which might be more common with feeding.
- INTRAVENOUS NUTRITION: All cooled babies need intravenous fluid (even when milk feeds are given it takes several days before enough fluid can be given this way). Some neonatal units give babies intravenous nutrition (which contains fat, protein, carbohydrate, vitamins and minerals) as this may improve growth and recovery. Other neonatal units only give intravenous dextrose with simple salts because of concerns that intravenous nutrition leads to more infections.

This study will compare these different ways of providing nutrition. It will use a research database called the National Neonatal Research Database (NNRD). In England, Scotland and Wales doctors and nurses looking after babies in neonatal care (including all cooled babies) use an Electronic Health Record system. Data from this system are anonymised (no baby can be identified) and form the NNRD, so the NNRD holds data from all babies who have been looked after on NHS neonatal units. We have worked closely with parents and charities in developing the NNRD.

We will use the NNRD to study all term babies who received cooling in England, Scotland and Wales since 2008. We will compare the milk feeding and intravenous nutrition they receive.

- MILK FEEDING: We will compare babies who are fed milk while cooled with those that are not fed any milk. Our main goal is to establish whether there is any difference in rates of necrotising enterocolitis.
- INTRAVENOUS NUTRITION: We will compare babies who get intravenous nutrition with those that only get intravenous dextrose. The main difference we are looking for is in the rate of infection. We will also study how many babies die, how long they stay in neonatal care, how soon breastfeeding starts and many are breastfed when they go home.

We will apply a statistical approach called “potential outcomes framework” in which babies are matched in each group (e.g. babies who are fed and those who are not fed) as closely as possible. This will ensure that any difference in outcomes is due to the different nutritional treatments and not due to background differences or other confounders (like how sick a baby is).

1. INTRODUCTION

1.1 BACKGROUND

Therapeutic hypothermia, cooling the whole body to 33-34°C for 72 hours, is the standard of care for infants with moderate-to-severe hypoxic ischemic encephalopathy (HIE) (1); this treatment has been recommended by NICE since 2010. Approximately 1200 babies receive therapeutic hypothermia annually in England, Scotland and Wales (unpublished data; National Neonatal Research Database (NNRD)).

Administration of therapeutic hypothermia itself (e.g. temperature, duration and rewarming) is well defined and follows a protocol based on high quality randomised controlled trials (1, 2). Optimal concurrent supportive care for infants while they receive therapeutic hypothermia is however, not evidence based. One contentious component of concurrent supportive care is provision of nutrition, including both enteral (milk) and parenteral (or intravenous) nutrition.

Normal healthy term babies would be expected to breast or bottle feed independently (or 'on demand') shortly after birth. Babies that receive therapeutic hypothermia for HIE cannot feed independently. They have suffered a hypoxic insult to their brain and other organ systems; they are often unable to coordinate sucking and swallowing safely, cannot regulate fluid balance (due to renal injury) or glucose metabolism (due to hepatic damage) often resulting in hypoglycaemia which can worsen brain injury. All babies receiving therapeutic hypothermia therefore will be commenced on intravenous fluid shortly after admission for neonatal care (3).

The intravenous fluid can be simple intravenous dextrose solution (with electrolytes such as sodium and potassium as required) or a more complex parenteral nutrition (PN) delivering protein, fat, vitamins, minerals and carbohydrate – this is the parenteral component of nutritional support.

Babies can be kept on only simple intravenous dextrose or parenteral nutrition while they are receiving therapeutic hypothermia (i.e. have no milk feeds), or they can be started on enteral (milk) feeds gradually – this is the enteral component of nutritional support.

Background and rationale for different enteral nutrition options

The reason that enteral (milk) feeds are withheld during therapeutic hypothermia is because of concerns about necrotising enterocolitis (NEC). Necrotising enterocolitis is a feared and often devastating condition that it is associated with considerable mortality and morbidity (4). While it is predominantly seen in preterm infants, it does occur in term babies with predisposing conditions such as HIE (5). The UK randomised TOBY trial of whole body hypothermia for HIE (2) reported one case of NEC (an infant in the hypothermia group) among 325 participants. The pathogenesis of NEC is incompletely understood; one putative mechanism links impaired gastrointestinal blood flow (seen in infants with HIE) and intraluminal substrate such as milk, as a trigger for the proinflammatory cascade and gastrointestinal necrosis that characterizes NEC (6, 7). Therefore, withholding enteral (milk) feeds is practiced to reduce the risk of developing NEC, despite an absence of evidence that withholding enteral feeds reduces the incidence of NEC (8).

The alternative approach, starting and gradually increasing enteral feeds while a baby is receiving hypothermia, is supported by limited animal and human physiological data. Animal studies indicate that hypothermia decreases inflammatory, histological and metabolic gastrointestinal damage by mechanisms such as reducing intestinal infiltration with neutrophils, alleviating oxidative stress by preventing overproduction of nitric oxide and by altering fatty acid metabolism pathways (9, 10). In humans, a study that compared infants who underwent therapeutic hypothermia with a historical cohort showed improved feeding tolerance and GI morbidity in the therapeutic hypothermia group (11). Infants in the therapeutic hypothermia cohort reached full enteral feeds significantly sooner than the infants in the historical cohort preceding therapeutic hypothermia. In summary, these limited studies suggest that following a hypoxic insult, hypothermia, may have a protective effect on the GI system. The potential benefits of starting enteral (milk) feeds during hypothermia include earlier establishment of full enteral feeds and earlier discharge home, improved feed tolerance, greater comfort for the baby and improved parental bonding.

Background and rationale for different parenteral nutrition options

Intravenous dextrose provides sufficient carbohydrate energy to prevent hypoglycaemia, but does not provide other nutritional components such as protein and fat; therefore infants will break down fat and muscle stores while they receive therapeutic hypothermia. Parenteral (intravenous) nutrition contains fat, protein, vitamins and essential trace minerals in addition to carbohydrate, and as such provides more complete nutritional support and limits catabolism. This is the rationale for giving parenteral nutrition to babies receiving therapeutic hypothermia: it will improve overall growth and potentially improve brain growth and development. This conjecture is not backed up by any human studies.

The counter-argument comes from the PEPaNIC trial (12), which raised the possibility that early provision of PN may be harmful. The PEPaNIC trial randomised 1440 critically ill children (including 209 term infants less than 28 days old) to receive PN within 24 hours of admission or for PN to be delayed until for 7 days. While mortality was similar between the two groups, children who had PN withheld for 7 days had a significantly lower rate of new infection (10.7% vs 18.5%). The late PN group also had a shorter hospital stay and shorter duration of ventilation. A post-hoc subgroup analysis of term infants less than 28 days old found that the benefits of late PN were similar or greater than the overall study group. The PEPaNIC trial was carried out on paediatric intensive care units, rather than neonatal units and so was unlikely to have included many (or potentially any) babies treated with therapeutic hypothermia for HIE. Therefore, the results cannot be extrapolated to this group. The PEPaNIC trial does however raise concerns about potential harms of early PN, and the findings are in keeping with similar studies in adult intensive care (13). Parenteral nutrition is an important contributor to the cost of neonatal care (14). If PN is not beneficial, or indeed harmful, in this group of babies, standardized, limited use of PN in this population would save the NHS money.

As yet, no trials have been performed to identify the best strategies to provide nutrition to infants with HIE during and after therapeutic hypothermia. Current UK feeding practices for these infants are therefore not supported by any evidence based guidelines and are very variable: A recent survey of UK Neonatal Intensive Care Units (NICUs) demonstrated wide variation in clinical practice (15). The survey, performed

in 2014, revealed that 45% of NICUs do not feed infants during therapeutic hypothermia, 40% feed depending on the clinical condition and the rest use trophic feeds or give incremental volumes of milk at different rates (15). In addition, 55% of units report routinely using parenteral nutrition while 6% report never using parenteral nutrition in this group of infants.

These findings are in keeping with the report of Thayagarajan et al. (3) which compared practice between two NICUs in Sweden and one NICU in the UK. Most Swedish infants (91%) were fed enterally during therapeutic hypothermia; in the UK only 33% received enteral feeding. This study did not find any difference in the time taken to reach full feeds between Swedish and UK neonatal units, but its small size (only 84 infants) and well known differences in feeding practices and attitudes between the two countries make it difficult to apply the results to the UK population (a significantly larger proportion of the Swedish cohort was exclusively breastfed). Finally, a very small single-centre observational study in the UK (25 infants) found no difference in time to reach full feeds by day or risk of gastrointestinal complications between infants fed and those not fed during therapeutic hypothermia (16).

1.2 RATIONALE FOR CURRENT STUDY

There is weak evidence that infants with HIE who undergo therapeutic hypothermia tolerate enteral feeding. There is insufficient evidence to recommend the optimal feeding strategy that would minimise gastrointestinal complications (such as NEC), expedite enteral feeding, and reduce the length of hospital stay. In relation to parenteral nutritional support, there is strong evidence from other population groups that early parenteral nutrition is harmful, but insufficient evidence to guide practice for babies with HIE.

There are two overarching uncertainties in the nutritional support of babies receiving therapeutic hypothermia:

1. **ENTERAL:** Some UK units gradually increase milk feeds while others omit all milk feeds. Potential benefits of milk feeds include greater comfort for the baby, earlier establishment full milk feeds, reduced intravenous therapy, fewer complications (such as infections), increased parental involvement in care and earlier discharge home.
Conversely, milk feeds may increase the risk of necrotising enterocolitis.
2. **INTRAVENOUS:** All babies treated with therapeutic hypothermia receive intravenous therapy; some UK units administer this as intravenous (parenteral) nutrition and some as intravenous dextrose. Parenteral nutrition may lead to better growth but may increase the risk of infection. The PEPaNIC trial (12) compared early with late parenteral nutrition in paediatric intensive care and found fewer infections among children who had no parenteral nutrition in the first week of intensive care.

2. STUDY OBJECTIVES

The overarching aim of this project is to determine the optimum enteral and parenteral nutrition strategy for newborns with HIE during and after therapeutic hypothermia.

2.1 RESEARCH QUESTIONS

We will perform two primary comparisons:

1. ENTERAL: the objective of this comparison will be to determine whether any enteral (milk) feeding, compared to withholding enteral feeding (no milk), during therapeutic hypothermia, is associated with a difference in the incidence of necrotising enterocolitis.
2. PARENTERAL: the objective of this comparison will be to determine whether provision of intravenous dextrose, compared to provision of parenteral nutrition, during therapeutic hypothermia, is associated with a difference in the incidence of blood stream infection.

2.2 HEALTH TECHNOLOGIES BEING ASSESSED

Current nutritional practice for babies receiving therapeutic hypothermia varies in the both enteral and parenteral (intravenous) components. This proposal will examine health technologies in enteral and parenteral aspects.

In the enteral component of nutrition, the health technology to be assessed is the gradual introduction of enteral (milk) feeds during therapeutic hypothermia:

- Included in this is any type of milk (e.g. expressed maternal breast milk, expressed donor breast milk and artificial formula)
- This health technology includes different routes of administering enteral feeds such as nasogastric tube (gavage feeding) and bottle
- This health technology also includes different rates of increasing enteral feeds (for example by 15ml/kg/day, by 30ml/kg/day or faster)

This enteral health technology will be compared against withholding enteral feeds (keeping a baby *nil per os*) for the duration of hypothermia.

In the parenteral component, the health technology being assessed is administration of parenteral nutrition during therapeutic hypothermia:

- Included in this are different compositions of parenteral nutrition (for example standard, pre-prepared bags of nutrition and individually tailored parenteral nutrition)
- This health technology includes different routes of administration of parenteral nutrition such as via a peripheral intravenous cannula, percutaneous central venous catheter ('long line') or umbilical venous catheter.
- This health technology also includes different volumes of parenteral nutrition (e.g. 40ml/kg/day, 60ml/kg/day or greater).

This parenteral health technology will be compared against standard intravenous fluids (10% dextrose with additional electrolytes added where required) for the duration of hypothermia.

3. STUDY DESIGN

Retrospective cohort study using existing data held in the National Neonatal Research Database (NNRD). The analysis will apply the potential outcomes framework using propensity score matching.

All analysis will be using anonymised data held in an approved research database, the NNRD. No patient identifiable information will be used in this study.

3.1 STUDY OUTCOME MEASURES

For the enteral comparison, the primary outcome will be necrotising enterocolitis defined according to the case definition of Battersby et al (17)

For the parenteral comparison, the primary outcome will be blood stream infection defined according to the Healthcare Quality Improvement Partnership (HQIP) National Neonatal Audit Programme (NNAP) case definition, which is determined using NNRD data

- The NNAP case-definition uses “pure growth of a recognised pathogen from a normally sterile site”
- The NNAP calculates and publishes data for blood stream infection on all English NHS neonatal units annually (18)

Secondary outcomes for both enteral and parenteral comparisons will include:

1. Survival: defined as alive at final neonatal unit discharge
2. Length of stay: defined as number of days between first neonatal unit admission and final neonatal unit discharge for surviving infants
3. Breastfeeding at discharge: defined as any breastfeeding (suckling at the breast) at discharge, this outcome is audited annually by the NNAP and data on method of feeding (differentiating for example “suckling at the breast” from “bottle feeding with expressed breast milk”).
4. Hypoglycaemia: defined as any diagnosis of hypoglycaemia recorded after therapeutic hypothermia is commenced and before the final neonatal unit discharge
5. Time to full feeds: defined as the number of days until an infant is recorded as not requiring any parenteral nutrition or fluid (i.e. no parenteral nutrition or intravenous dextrose)
6. Growth: weight for post-menstrual age standard deviation score at final neonatal unit discharge

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

There will be no active recruitment of patients as this is an epidemiological study using routinely recorded, anonymised data held within an established research database, the NNRD.

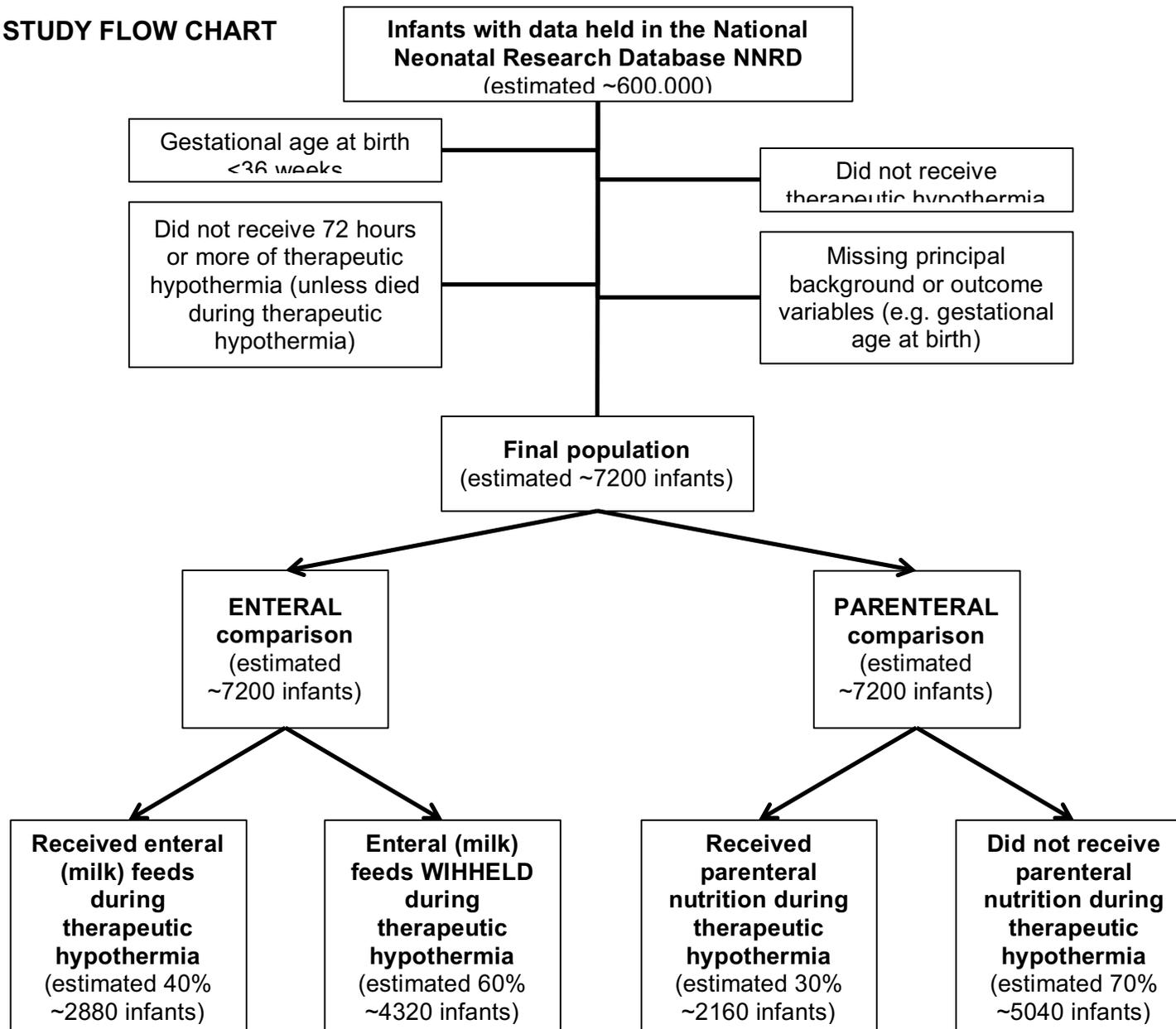
Eligible infants within the NNRD:

1. Received neonatal care at a unit that is part of the UK Neonatal Collaborative; this includes all NHS neonatal units in England, Scotland and Wales
2. Recorded gestational age at birth ≥ 36 weeks
3. Recorded as receiving therapeutic hypothermia for 72 hours or died during therapeutic hypothermia

4.2 EXCLUSION CRITERIA

Infants with missing data for principal background and outcome variables. Missing values for other variables will be dealt with using multiple imputation.

4.3 STUDY FLOW CHART



5. ASSESSMENT AND FOLLOW-UP

There will be no assessment or follow-up.

5.1 TIME PERIOD

NNRD data will be extracted for the period January 1st 2008-December 31st 2016 (9 years)

6. DATA ANALYSIS

Anonymised data held within the NNRD will be used for this study.

6.1 DATA SOURCE

National Neonatal Research Database (NNRD): the NNRD holds data from all infants admitted to NHS neonatal units in England, Scotland and Wales (approximately 90,000 infants annually). The NNRD is formed from data extracted from the neonatal electronic health record system used by health professionals during routine clinical care. This study will use routinely collected data.

Briefly, daily clinical information on neonatal unit admissions is recorded in a point-of-care, clinician-entered Electronic Patient Record. A defined data extract, the Neonatal Dataset (NHS Information Standard SCCI595) is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster NHS Foundation Trust where patient episodes across different hospitals are linked, data are cleaned, and entered into the NNRD (19). Contributing neonatal units are known as the UK Neonatal Collaborative (UKNC).

The NNRD holds the Neonatal Data Set, approximately 450 data items that form a NHS data standard (20). Data items include demographic and admission items (e.g. maternal conditions, birthweight), daily items (entered every day for all infants, e.g. respiratory support, feeding information), discharge items (e.g. feeding and weight at discharge) and ad hoc items (entered if and when they occur e.g. suspected infection, ultrasound scan findings, abdominal x-ray findings).

Data extracted from the neonatal Electronic Health Record are cleaned; records with implausible data configurations are queried and corrected by the treating clinicians. Cleaning is carried out by the Neonatal Data Analysis Unit before data are incorporated into the NNRD. The robustness of core NNRD data (birth weight, sex, length of stay and death) has been previously demonstrated for research purposes (21, 22). Data held in the NNRD are used for multiple purposes including national audit (the HQIP funded NNAP) and analyses for the Department of Health, NHS England and the Chief Medical Officer.

A formal comparison of NNRD data items against those recorded in Case Record Forms of a multicentre, randomised placebo controlled trial (Probiotics in Preterms, NIHR HTA 05/501/04 (23)) was undertaken as part of a NIHR Programme Grant for Applied Research (RP-PG-0707-10010); this work (submitted for publication) demonstrated a high degree of data agreement (>95%) between the NNRD and clinical trial Case Report Forms for core variables: e.g. 98.3% (95% CI 97.4-99) concordance for birth weight, 98.9% (98.1-99.4) concordance for instrumental delivery, 96% (95.1-96.8) concordance for length of neonatal unit stay, 99.4% (98.9-

99.8) concordance for antibiotic administration and 99.8% (99.4-99.98) concordance for survival to neonatal discharge.

Similar methods to those in the UK Neonatal Collaborative NEC Study (17) will be used to identify infants with NEC. These involve using daily, diagnostic, Abdominal X-ray and procedural variables held on the NNRD and verifying these patient-level data with study leads.

6.2 STATISTICAL METHODS

In each analysis (enteral and intravenous), we will apply the potential outcomes framework (24) to estimate the average effect of a treatment over its alternative. In this framework, a subset is found within each treatment group so that the two subsets have nearly identical distributions of all the background variables. This can be motivated as post-observational design (25), arranging the data so that they have the appearance of having arisen in a randomised study and can be analysed by methods appropriate for such studies. In particular, the two subgroups can be compared straightforwardly (by their means, medians, or the like), without any involvement of the background variables. This is an important conceptual strength of the framework. The analysis comprises two parts: in the first, matched subgroups are formed using only the treatment and background variables, without any involvement of the outcome variables; in the second, these subgroups are analysed without any involvement of the background variables. The treatment indicator is the sole link of the two parts.

Usually the first part is complex and time-consuming because it entails modelling of the selection process – the association of the treatment assignment to the background variables. We propose to do this by propensity analysis. Its output is the fitted propensities – fitted probabilities of being assigned a treatment as a function of the background variables. The matched subgroups are formed through matched pairs of infants, one from each treatment group. The propensity model is chosen so as to achieve a fine balance of the two subgroups. The theoretical support for this method is provided by (26) and (27).

A key prerequisite for successful matching is an extensive set of background variables that cover all aspects of potential confounding. While no set of variables can be confirmed as complete in this regard, we believe that we can extract from the NNRD a set of background variables that is much richer and has a higher degree of completeness than could be achieved by using an alternative source of data or an alternative method of data collection. The large sample (or population) size is another strength of our approach.

6.2.1 DATA VARIABLES TO BE INCLUDED IN PROPENSITY SCORE MATCHING

The following variables will be matched between comparator groups:

1. Demographic data items
 - a. Gestational age week
 - b. Birthweight standard deviation quartile
 - c. Sex
 - d. Multiplicity
2. Maternal factors
 - a. Maternal age

- b. Maternal prolonged rupture of membranes (>24 hours)
 - c. Maternal suspected chorioamnionitis
- 3. Infant factors: resuscitation
 - a. Apgar score at 5 minutes
 - b. Chest compressions administered
 - c. Emergency resuscitation drugs administered
 - d. Intubated at resuscitation
 - e. Umbilical cord pH
- 4. Infant factors: condition on neonatal unit prior to therapeutic hypothermia
 - a. Admission mean blood pressure
 - b. Treatment for low blood pressure with an intravenous inotrope (e.g. dopamine, noradrenaline)
 - c. Admission blood glucose
 - d. Admission heart rate
 - e. Admission oxygen saturation
 - f. Ventilation
 - g. Admission temperature
 - h. Umbilical venous line in situ
 - i. Umbilical arterial line in situ
- 5. Organisational factors
 - a. Required postnatal transfer (Y/N)
 - b. Neonatal network

Treatments that occur after neonatal unit admission will not be matched as these are not independent of the health technology being assessed (nutrition during therapeutic hypothermia).

Logistic regression model is fitted to the treatment (a dichotomous variable) in terms of the background variables. The model is supplemented by transformations of the continuous background variables and by interactions with the purpose of obtaining a good balance. The fitted propensities (probabilities of being assigned the focal treatment) for the babies in the study are divided into percentiles (100 *propensity* groups), or pairs of percentiles (50 groups), and matched pairs are formed within these groups; in each pair, there is one baby from either treatment group. The babies in these matched pairs are re-formed as two treatment subgroups and their balance on all the background variables is assessed by means of a balance plot; see supplementary materials in (22) for an example. The logistic regression model is reviewed (an interaction or transformation term added to it) and the balance plot constructed. This procedure is iterated until no improvement in the balance can be achieved. The 'final' logistic model has no interpretation; its sole purpose is to construct two treatment subgroups of babies that have similar distributions of the background variables, so that they have the appearance of having been obtained by a randomised study. These two subgroups are then analysed by methods that would be appropriate for a randomised study. The sampling variance of the estimator of the average treatment effect is estimated from replicate matched treatment groups as the sum of the average of the estimated sampling variances for the replicates and the adjusted (inflated) variance of the estimates across the replicates. Details are given in Appendix 1 (Rubin's rule)

6.2.2 SUBGROUP AND SENSITIVITY ANALYSES

Sensitivity analysis will be conducted by constructing an additional background variable, a dichotomy, in such a way as to stack the odds against the treatment inferred to be superior. This can be done for a range of odds ratios. We will find the borderline odds ratio, for which the treatment effect vanishes, or becomes not significant (as appropriate). Then we'll pose the question whether, in view of the background variables used in the analysis, it is plausible that there might be such a binary variable missing from the list of background variables.

In relation to missing background (confounder) variables, where the proportion of missing entries for a variable is substantial, we will form matched subgroups by regarding nonresponse as a separate category for a categorical variable or a binary variable for continuous variable. In addition, when a principal (important) background variable has many missing entries, we will conduct a sensitivity analysis by imputing for these missing entries values generated according to a missing not at random mechanism that is stacked against the original conclusion of the analysis, exploring pessimistic scenarios.

6.2.3 SAMPLE SIZE

It is estimated that approximately 7200 infants whose de-identified data are held in the NNRD will meet the study inclusion criteria.

Pilot data extracted from the NNRD shows the approximate spread of infants receiving different nutritional therapies in 2014 and 2015, tables 1 and 2.

Year	Number of babies in cohort	Number (%) of babies receiving any enteral feeds	Number of babies where enteral feeds were withheld
2014	796	301 (38)	495 (62)
2015	809	320 (40)	489 (60)

Table 1: Infants treated with therapeutic hypothermia in England, Scotland and Wales who received different enteral nutrition strategies

Year	Number of babies in cohort	Number of babies receiving Parenteral Nutrition	Number of babies not receiving parenteral nutrition
2014	796	250 (31)	546 (69)
2015	809	238 (29)	571 (71)

Table 2: Infants treated with therapeutic hypothermia in England, Scotland and Wales who received different parenteral nutrition strategies

Assuming the proportions of infants receiving different enteral and parenteral nutrition options is similar to that seen in pilot data (tables 1 and 2), a sample size of 7200 infants receiving therapeutic hypothermia will detect (two-sided significance 5%, power 90%) a difference of:

- 0.7% in NEC with 2000 matched pairs, assuming that the rate of NEC is negligible in the reference treatment

- 2% blood stream infection with 1500 pairs, assuming that the rates of BSI are 1% and 3%

6.2.4 MISSING DATA

Imputation will be applied to deal with missing values. Single imputation will be applied only when the fraction of the missing items is negligible, otherwise multiple imputation will be applied. List-wise deletion will be applied only to records that are missing the majority of entries relevant to the analysis.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL

This study will be carried out using data held in the Neonatal Research Database (NNRD). The NNRD holds derived from operational electronic neonatal data.

The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee (REC) approval, 16/LO/1093, and Confidential Advisory Group (CAG) approval, ECC 8-05(f/2010), to form the National Neonatal Research Database (NNRD).

Research applications to access the NNRD from members of the NDAU (including this proposal) are covered within the existing REC approval (16/LO/1093), pending the approval of the Director of the Neonatal Data Analysis Unit, the Neonatal Data Analysis Unit Steering Board and the 200 neonatal units that form the United Kingdom Neonatal Collaborative (UKNC).

Approval for this study was granted by the NDAU director and board (at the steering group meeting 11th October 2016).

Approval from the UKNC will be obtained through a well-established process administered by the NDAU, whereby neonatal units are offered the opportunity to opt-out of their unit's data being used for this study (to date, no UKNC unit has opted out of their unit's data being used for an academic study).

The Chief Investigator has obtained approval from the HRA. The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study. 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

This study will only use anonymised data held in an established research database, the NNRD.

7.3 CONFIDENTIALITY

Only anonymised data will be used in this study.

7.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Gallagher London negligent (public liability) and non-negligent harm (no fault) policy number: B1262FI0114916.

7.5 SPONSOR

Imperial College London

7.6 FUNDING

The study is funded through NIHR HTA grant 16/79/03.

8. STUDY MANAGEMENT

An independent Study Steering Committee (SSC) will be appointed by the study funder (NIHR). This will include the Chief Investigator (Dr Gale), an independent chair, and independent statistician and a parent/patient representative. The SSC will meet before the end of month 2 of the study and again in the second year of the study.

A Clinical Investigator Group (CIG) will be formed of all members of the project team. The CIG will meet 3 times:

1. At the end of month 1 to agree the final protocol and data extraction plan
2. At the end of month 6 to review the data extraction and analysis plan
3. At the end of month 13 to review analysis results, discuss conclusions, agree write up and dissemination strategy

A core study management group consisting of CG and NL (Co-Chief Investigators) will meet at least monthly throughout the study to co-ordinate the project with other members of the team co-opted as deemed appropriate. Where necessary, decisions will be referred to the steering group. Administrative support, for example contacting United Kingdom Neonatal Collaborative (UKNC) units, will be provided by the Neonatal Data Analysis Unit (NDAU).

9. PUBLICATION POLICY

The results of this study will be reported as a manuscript in a peer-reviewed scientific journal. All members of the study group will be authors with additional contributors as appropriate. Publications will acknowledge the NIHR and NNRD as set out in relevant guidance.

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Record of changes

V1.3, 24/7/17: addition of trial registration information on page 1

V1.4, 28/7/17: change of study management to include NIHR mandated independent Study Steering Committee; co-investigator group now formed into Clinical Investigator Group (CIG).