

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
COLLABORATE

1. Is your project research?

☒ Yes ☐ No

2. Select one category from the list below:

- ☐ Ionising Radiation for combined review of clinical trial of an investigational medicinal product
- ☐ Ionising Radiation and Devices form for combined review of combined trial of an investigational medicinal product and an investigational medical device
- ☐ Clinical investigation or other study of a medical device
- ☒ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- ☐ Basic science study involving procedures with human participants
- ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ☐ Study involving qualitative methods only
- ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- ☐ Study limited to working with data (specific project only)
- ☐ Research tissue bank
- ☐ Research database

If your work does not fit any of these categories, select the option below:

☐ Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

☐ Yes ☒ No

2b. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation? ☐ Yes ☒ No
- b) Will you be taking new human tissue samples (or other human biological samples)? ☒ Yes ☐ No

c) Will you be using existing human tissue samples (or other human biological samples)? ☐ Yes ☒ No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- ☒ England
☒ Scotland
☒ Wales
☒ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ☒ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ This study does not involve the NHS

4. Which applications do you require?

- ☒ IRAS Form
☐ Confidentiality Advisory Group (CAG)
☐ HM Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

- ☒ Yes ☐ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research, e.g. NHS support costs) for this study provided by an NIHR Biomedical Research Centre, NIHR Applied Research Collaboration, NIHR Patient Safety Research Collaboration, or an NIHR HealthTech Research Centre in all study sites?

Please see information button for further details.

- ☐ Yes ☒ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Research Delivery Network (RDN) Support and inclusion in the NIHR RDN Portfolio?

Please see information button for further details.

- ☒ Yes ☐ No

The [NIHR Research Delivery Network \(RDN\)](#) enables the health and care system to attract, optimise and deliver research across England e.g. by supporting the successful delivery of high-quality research, as an active partner in the research system.

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR RDN.

6. Do you plan to include any participants who are children?

☒ Yes ☐ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

☐ Yes ☒ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

☐ Yes ☒ No

9. Is the study or any part of it being undertaken as an educational project?

☐ Yes ☒ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

☐ Yes ☒ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

☐ Yes ☒ No

Integrated Research Application System
Application Form for Other clinical trial or investigation**IRAS Form (project information)**

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
COLLABORATE

Please complete these details after you have booked the REC application for review.

REC Name:

London - Bloomsbury Research Ethics Committee

REC Reference Number:

25/LO/0697

Submission date:

26/08/2025

PART A: Core study information**1. ADMINISTRATIVE DETAILS****A1. Full title of the research:**

An efficient, UK-wide, real-world-data-enabled, adaptive, 2-randomisation, controlled trial to determine clinical efficacy, effect size, and safety of widely used enteral feeds in reducing necrotising enterocolitis, mortality, and cognitive impairment in preterm babies born below 29 weeks gestation

A3-1. Chief Investigator:

	Title Forename/Initials Surname
	Prof Neena Modi
Post	Professor of Neonatal Medicine, Consultant in Neonatal Medicine
Qualifications	MB ChB; MD; FRCP; FRCPCH; FMedSci
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Work Telephone 07525611677

* Personal Telephone/Mobile 07525611677

Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title Forename/Initials Surname
	Ms Ruth Nicholson
Address	Imperial College London, Research Governance Integrity Team 5th Floor, Sherfield Building, South Kensington Campus London
Post Code	SW7 2BB
E-mail	r.nicholson@imperial.ac.uk
Telephone	02075941862
Fax	

A5-1. Research reference numbers. Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number: 181495

Protocol Version: 1.0

Protocol Date: 22/08/2025

Funder's reference number (enter the reference number or state not applicable): NIHR EME:163188

Project website: <https://www.imperial.ac.uk/neonatal-data-analysis-unit/collaborate/>

Registry reference number(s):

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number	Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

☐ Yes ☒ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

The COLLABORATE study will address two uncertainties in the care of babies born less than 29 weeks gestation. First whether pasteurised human donor milk or preterm formula, when used to supplement insufficient availability of milk from a baby's own mother, and second whether routine versus no routine fortification of human milk feeds, affects survival to 34 weeks postmenstrual age without requiring surgery for necrotising enterocolitis. Necrotising enterocolitis is an acquired inflammation of the intestinal tract and a major cause of death and long-term impairment in preterm babies.

We will also evaluate a range of important secondary outcomes and associated hospital costs. The study additionally includes an embedded sub-study that will use magnetic resonance imaging (MRI) and serial stool sampling to determine whether donor milk and formula have different effects on development.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Consent:

This study compares interventions that are already in widespread use, hence verbal consent will be sought following provision of information and opportunity to ask questions.

Verbal consent will be documented in the eCRF and medical records by the member of the clinical care team who has explained the study and sought consent. A paper verbal consent statement will be used as a back-up.

The parents/legal guardians of all eligible babies will be given the parent information sheets and will be given adequate time before deciding whether they want their child to participate.

All parents/legal guardians will have capacity to consent. If capacity to consent is lost during the study, the participants would remain included as the interventions are in widespread use and a legal guardian will always be in place.

Participants will be provided with a copy of the signed Participant Information Sheet/Verbal Consent Form document.

The original paper Verbal Consent Form will be retained with the source documents.

Written informed consent will be sought for the mechanistic sub-study as this involves a magnetic resonance imaging scan and/or stool samples obtained solely for research purposes.

Rationale

This study is needed because the types of enteral feeds an extremely preterm baby receives, namely fresh Own Mother's Milk, pasteurised Human Donor Milk (pHDM), preterm formula, and macronutrient fortifier, are widely believed to influence the risk of necrotising enterocolitis (NEC), an acquired inflammation of the immature gastrointestinal tract and leading cause of death and life-long impairment in extremely preterm babies. There are around 3000 babies born <29 weeks gestation, and around 260 NEC deaths and/or surgeries each year in the UK, with up to 3 times more developing less severe disease that nonetheless disrupts feeding, prolongs hospital stay, and increases antibiotic exposure, and costs of care.

Own Mother's Milk is standard of care for all newborn babies and reduces but does not totally prevent NEC. The developmental ability to suckle effectively is not reached until 33-34 weeks gestation, hence their mothers must express breast milk for many weeks which they report as stressful and difficult to sustain. Therefore, over 85% of extremely preterm babies require supplementary feeds. In the UK, around a third of extremely preterm infants requiring supplementary feeds receive pHDM and around two-thirds receive Preterm Formula.

Early nutrition is a prime determinant of learning ability, through direct nutritional effects on brain development, the non-nutritional components of human milk, and indirectly through influencing the risk of NEC and attendant physical and neurodevelopmental consequences.

Preterm Formula has consistent composition whereas human milk has low and variable nutrient content. This is

especially an issue for pHDM as breast milk nutrient content is lower in mothers delivering at full-term compared to preterm, and declines with lactation duration, and donors have generally delivered at full-term and have been lactating for several weeks. Routine addition of macronutrient fortifier may be necessary but equally may expose babies to excessively high protein intakes, dangerous to neurodevelopment, renal, and metabolic health. In the UK, around half of extremely preterm babies receive fortified feeds.

Own Mother's Milk and pHDM are not equivalent as not only is human milk very variable in nutrient and non-nutrient content, but composition is unique to each mother, and pasteurisation substantially reduces or destroys biologically active non-nutritional components.

This study will address the longstanding unmet health need of the daily uncertainty faced by healthcare professionals and parents in the UK and around the world around the efficacy and safety of pHDM, Preterm Formula and Fortifier in relation to the risk of NEC. Decisions about these feeds affect extremely preterm babies, every day, in the UK and worldwide. The uncertainties are a major clinical concern and have led to highly variable practice, anxiety for parents, confusion for staff, and risks to patient safety. The study is also needed to establish value for money, given the large cost difference between pHDM (£125-£200 per litre), Preterm Formula (£5 per litre), fortifier (£5/litre of human milk fortified), and the high cost of NEC treatment.

Risk Benefit Assessment

There is fear that highly processed cow-milk based products (Preterm Formula and Fortifier) may be damaging to the immature intestinal mucosa and increase the risk of NEC. There is also fear that without these products, nutrient intake will be inadequate.

Also of concern are safety signals; the most recent randomised controlled trial comparing pHDM and Preterm Formula to supplement Own Mothers Milk, the Canadian Domino Trial, found higher neuro-impairment at 18 months in the pHDM arm (27.2% v 16.2%; Adjusted Risk Difference 10.6% [95% CI 1.5%, 19.6%]) and a worse mortality/morbidity index (43% v 40%). In a causal inference analysis of 5 years UK population-based observational data, we found almost 10% lower survival without NEC surgery to 34 weeks gestational age (Adjusted Risk Difference -9.8% [95% CI -11.4, -8.2]) and a surgical NEC rate that was twice as high in very preterm infants receiving supplemental pHDM, compared with Preterm Formula. These unexpected, counterintuitive findings may reflect unmeasured confounding (i.e., clinician tendency to use pHDM in infants they consider more at risk of NEC) but nonetheless are also justification for a randomised trial.

Recruitment

This study will take place at approximately 80 Neonatal Intensive Care Units and Local Neonatal Units in England, Scotland, Wales, and Northern Ireland. The remaining 101 NHS neonatal units in the UK may be involved as step down sites. The study involves two randomisations. Sites and babies may participate in either or both randomisations. In randomisation 1, we will compare the benefits of supplementation with either pHDM or Preterm Formula if the available volume of Own Mother's Milk is insufficient. In randomisation 2 we will assess the benefits of routine fortification of human milk versus consideration of fortification only if a baby meets pre-defined criteria.

Burdens

There will be no research-related procedures or evaluations except for infants participating in the embedded mechanistic sub-study, who will be invited for brain MRI which is a well-established procedure, and serial stool sample collection. Standard Operating Procedures for ensuring safety in the MRI environment in place in the Edinburgh Imaging facility will be followed.

Upon discharge there are no research-related follow-up visits. Age 2-year cognitive and language outcomes will be obtained using the PARCA-R conducted as a component of routine clinical care. A digital option for completion of this questionnaire will be provided as part of COLLABORATE.

Extracting trial data from routinely available clinical information

COLLABORATE is a real-world data-enabled trial; this means that the majority of trial data will be obtained from clinical information entered into an existing neonatal EPR at the point of care and subsequently held, following quality-assurance and curation in the National Neonatal Research Database (NNRD), an established research database. All neonatal units in England, Scotland, and Wales contribute data to the NNRD, NNRD data are an NHS Information Standard (ISB1595). The NNRD is approved by the Caldicott Guardians and Lead Clinicians of all contributing neonatal units, the National Research Ethics Service (16/LO/1093) the Confidentiality Advisory Group of the Health Research Authority (805(f)/2010) and the Scottish Public Benefit and Privacy Panel. The quality and completeness of data that will be used in COLLABORATE have been validated against clinical paper notes and clinical trial Case Report Forms and high levels of agreement have been shown. All parents of babies admitted to neonatal units are given an information sheet that explains the NNRD and its uses (service evaluations, audit and approved research) and that if they wish they may choose to opt-out of inclusion of their baby's data in the NNRD. Extracting trial data in this way will be more efficient than conventional, duplicative, data collection and will increase value and reduce waste in research.

3. PURPOSE AND DESIGN OF THE RESEARCH**A7. Select the appropriate methodology description for this research. Please tick all that apply:**

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☒ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

In babies born <29 weeks gestation for whom there is need to supplement Own Mother's Milk, does donor milk, when compared with Preterm Formula, improve survival rate to 34 weeks gestational age without requiring surgery for NEC?

In babies born <29 weeks gestation, does routine macronutrient fortification of human milk (Own Mother's Milk and donor milk) with cow milk fortifier, when compared with no routine fortification, improve survival rate to 34 weeks gestational age without requiring surgery for NEC?

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

In babies born <29 weeks gestation for whom there is a need to supplement Own Mother's Milk, does donor milk, when compared with Preterm Formula, differ in effect on brain development assessed at using magnetic resonance imaging at full-term?

In babies born <29 weeks gestation for whom there is a need to supplement Own Mother's Milk, does the additional cost of donor milk, when compared with Preterm Formula, generate savings through improved survival to 34 weeks gestational age without requiring surgery for NEC?

In babies born <29 weeks gestation for whom there is a need to supplement Own Mother's Milk, does donor milk, when compared with Preterm Formula, and routine versus no routine fortification of human milk, affect a range of secondary growth and clinical outcomes?

A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.

The evidence for whether donor milk or formula is the better supplement is unclear, as is whether extremely preterm babies fed human milk routinely need extra protein and carbohydrate (Fortifier). Some clinicians fear that highly processed cow-milk based formula and fortifier might increase the risk of NEC; others fear that without fortification human milk is inadequate for optimal growth and brain development.

We searched the Cochrane Central Register of Controlled Trials for reviews and meta-analyses of published studies, and clinical trial registries for ongoing or recently completed trials (ISRCTN Registry; World Health Organisation International Clinical Trials Registry Platform; ClinicalTrials.gov). Collectively, these show there is inadequate evidence of efficacy and safety for the interventions.

This research is needed now because the uncertainties have led to current practice that is highly variable, and a proliferation of non-evidenced based guidelines. Parents, patients (those living with the long-term consequences of neonatal conditions), clinicians, and the James Lind Priority Setting Partnership have repeatedly ranked identification of enteral feeding strategies that reduce NEC a priority for well over a decade. The NICE guidance "Donor milk banks: service operation" acknowledges the limited high-quality evidence for use of donor milk and includes the recommendation for research to evaluate efficacy in improving outcomes and identify babies who would benefit most. The 2023 British Association of Perinatal Medicine "Framework for use of Donor Milk" also highlights the urgent need for this research. The American Academy of Pediatrics and European Society for Paediatric Gastroenterology, Hepatology and Nutrition only conditionally support use of donor milk as the supplementary feed of choice, acknowledging the benefits of own mother's milk over donor milk, the variable nutrient content and uncertain non-nutrient benefits of donor milk, and the limited evidence-base for practice.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Design

An adaptive, UK-wide, real-world-data-enabled, digital technology-facilitated, 2-randomisation, open-label, controlled trial embedded in routine clinical care. The study includes an internal pilot to assess rates of recruitment, co-randomisation, and withdrawal of consent, and includes formal interim efficacy monitoring

Location

This study will recruit from approximately 80 Neonatal Intensive Care Units and Local Neonatal Units in England, Scotland, Wales, and Northern Ireland with the remaining NHS neonatal units offered opportunity to participate as step down sites (sites taking part in the continued care of babies but not recruiting participants). Babies may participate in either or both randomisations. Babies will be assessed for eligibility by a member of the clinical care team (an appropriately trained and experienced neonatal doctor or nurse) after admission to the neonatal unit. There are no screening or pre-randomisation procedures. The primary outcomes will be assessed at 34 weeks postmenstrual age, however data will continue to be collected until the participant is discharged.

Consent and randomisation

As this study compares interventions that are already in widespread use, verbal consent will be sought. After consent, participants will be randomised. Randomisation 1 to donor milk or formula, will occur when the clinician decides a supplemental feed is required because the volume of own mother's milk is insufficient. Randomisation 2, to routine fortification or no routine fortification, will occur when the baby is receiving between 60-120 ml/kg/day of human milk feeds (Own Mother's Milk and/or donor milk).

Procedures

There will be no research-related procedures except for infants participating in the mechanistic sub-study, who will be invited for brain MRI at term equivalent age (38-42 weeks) which is a well-established procedure plus serial stool sample collection.

After the infant is discharged, there are no research-related follow-up visits. Age 2-year cognitive and language outcomes will be obtained using the PARCA-R conducted as a component of routine clinical care. A digital option for completion will be provided as part of COLLABORATE.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☒ Design of the research
- ☒ Management of the research
- ☒ Undertaking the research
- ☐ Analysis of results
- ☒ Dissemination of findings
- ☐ None of the above

Give details of involvement, or if none please justify the absence of involvement.

Parents and former patients have ranked identifying the best way to feed preterm babies to prevent NEC a priority for

over a decade.

Patients, parents, and carers have been actively involved in COLLABORATE and our dedicated Parent, Patient, and Public Involvement and Engagement (PPPIE) lead will ensure continuing involvement supported by co-investigators Bliss (the national preterm and sick baby charity), APAN (Adult Premie Advocacy Network), collaborating organisation, NEC UK (national charity), and two community partners, people with experience of neonatal care that have strong links with and a passion for improving the health of their communities.

We have held PPPIE workshops to discuss the study and ensure equity in participation. Parents and former patients chose the name, COLLABORATE, and created the logo. PPPIE has played an integral part in the development of this proposal through focus groups and one-to-one discussions. We involved parents in the development of a digital version of the PARCA-R, a validated questionnaire to assess language and cognitive development at age 2-years. Parents helped evaluate ease of use, acceptability, and consent for data sharing. The digital PARCA-R will be made available to neonatal units as part of COLLABORATE. They helped us co-create an initial version of a Parent Information Leaflet which consists of a short explanatory paragraph on the first page and more detailed information on the back, that can be read at a time and pace suited to everyone. Parents will also be provided with a separate privacy notice explaining how we will handle their data. Parents also suggested we provide short video clips voiced by parents that explain COLLABORATE and their support for the study.

PPPIE members will attend committee meetings (Trial Management; Trial Steering; Data Monitoring and Ethics; Emerging Investigator; PPPIE Advisory), review participant information, communication, and dissemination materials, and community partners will act as Equality, Diversity and Inclusion leads.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☒ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory

- ☐ Skin
- ☐ Stroke

Gender: Male and female participants

Lower age limit: Weeks gestational age

Upper age limit: 29 Weeks gestational age

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Randomisation 1

Inclusion criteria

- Born <29 weeks gestation
- No condition precluding enteral feeding
- Maternal intention to express breast milk
- The parent's verbal consent for the baby to participate in the trial has been documented in the baby's medical notes and Investigator Site File (ISF)

Randomisation 2

Inclusion criteria

- Born <29 weeks gestation
- No condition precluding enteral feeding
- Maternal intention to express breast milk
- The parent's verbal consent for the baby to participate in the trial has been documented in the baby's medical notes and Investigator Site File (ISF)

Mechanistic study

- Participants in randomisation 1 recruited at the Royal Infirmary of Edinburgh
- Written informed consent for the mechanistic study

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Randomisation 1

Exclusion criteria

- Baby has already received pHDM, Preterm Formula

Randomisation 2

Exclusion criteria

- Baby has already received Fortifier

Mechanistic study

- Infants with congenital anomalies: structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life (WHO definition)
- Infants with a contraindication to MRI at 3Tesla.

RESEARCH PROCEDURES, RISKS AND BENEFITS
A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4

Verbal consent	1	0	15	Trained and delegated member of the research team at the participating site
Written informed consent - Mechanistic sub-study	1	0	15	Trained and delegated member of the research team at the participating site
PARCA-R questionnaire	1	0	20	Completed by parents on paper or electronically (part of standard routine care)
Participant identification and eligibility check	3	0	15	Trained and delegated member of the research team at the participating site
Record of adverse events	3	0	5	Trained and delegated member of the research team at the participating site
Randomisation	2	0	5	Trained and delegated member of the research team at the participating site

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Randomisation 1: pasteurised HDM supplement to mothers milk (the number of feeds per participant is not possible to determine)	UNK	All	N/A	Clinical team (Doctors and nursing staff) caring for infant on neonatal unit; number of interventions depend on the number of days in hospital.
Randomisation 1: formula supplement to mothers milk (the number of feeds per participant is not possible to determine)	UNK	All	N/A	Clinical team (Doctors and nursing staff) caring for infant on neonatal unit; number of interventions depend on the number of days in hospital.
Randomisation 2: fortification of human milk feeds (the number of feeds per participant is not possible to determine)	UNK	All	N/A	Clinical team (Doctors and nursing staff) caring for infant on neonatal unit; number of interventions depend on the number of days in hospital.
Randomisation 2: treatment as usual (the number of feeds per participant is not possible to determine)	UNK	All	N/A	Clinical team (Doctors and nursing staff) caring for infant on neonatal unit; number of interventions depend on the number of days in hospital.
Magnetic resonance imaging (only for participants consented to the	1	0	60	Clinical research team at

sub-study)

Royal Infirmary Edinburgh

Stool sample collection (Edinburgh participants only) (range from 7 to 14 0 10 14 to cover gestational age range 22-29 weeks with sampling from week 1 to 34 weeks plus one at term equivalent age (MRI).

Clinical research team at
Royal Infirmary Edinburgh

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

☐ Yes ☒ No

A21. How long do you expect each participant to be in the study in total?

Participants will be in the study from birth up to age 2 years (corrected for prematurity).

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

All randomised arms are used in standard feeding of preterm babies. As there are no research related procedures (except MRI in the sub-study) there are no risks or additional burden to the patients.

For the participants in Edinburgh who will take part in the mechanistic sub-study, the MRI scanner makes a loud knocking noise, so earmuffs are used to prevent noise discomfort and encourage infants to sleep. We will use established procedures that ensure infant safety and physiological stability during imaging. The infant will have continuous monitoring of vital signs (heart rate and oxygen saturation) with an electronic monitor. The attending clinician will record observations every 5 minutes until 1 hour after the infant has woken up, and the scan will be stopped if there are any abnormalities in monitoring. Full neonatal resuscitation facilities are available on site. Standard Operating Procedures for ensuring safety in the MRI environment in place in the Edinburgh Imaging facility will be followed.

Incidental findings can also occur from the MRI scans. We will refer any incidental findings that may be clinically actionable to the child's general practitioner and any relevant NHS services through the clinical care team.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☐ Yes ☒ No

A24. What is the potential for benefit to research participants?

Individuals taking part in a randomised controlled trial receive care in a closely monitored pathway and may benefit regardless of the arms to which they are randomised (inclusion benefit). Individuals will also benefit through allocation of treatment by randomisation which ensures every individual baby has a fair and equal chance of receiving the (unknown) best treatment option.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

There are no arrangements required for the continued provision of the intervention. Once discharged the babies will no longer require the interventions.

A26. What are the potential risks for the researchers themselves? (if any)

There are no risks associated with the researchers. All study related procedures will be completed at the participating

site in the presence of other site personnel.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Babies will be assessed for eligibility by a member of the clinical care team (an appropriately trained and experienced neonatal doctor or nurse) after admission to the neonatal unit.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☒ Yes ☐ No

Please give details below:

The clinical care team will review medical records of participants admitted to the neonatal unit to check whether they meet the inclusion criteria and make the initial approach to parents/legal guardian.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants. *Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Only clinical care team members will review medical records. The participants' parents will be provided with a privacy notice detailing how their child's data is processed while in the study.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

☒ Yes ☐ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

☒ Yes ☐ No

If Yes, please give details below.

Consent will be sought to obtain NHS/CHI/H&C number for accessing long term outcome records from NHS Digital or similar organisations. NHS number can also be used to cross check data obtained from the NNRD record.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☐ Yes ☒ No

A29. How and by whom will potential participants first be approached?

Parents/guardians will be approached by a member of the clinical care team after the baby's admission to the

neonatal unit.

A30-1. Will you obtain informed consent from or on behalf of research participants?

☒ Yes ☐ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Verbal consent will be sought as this study compares interventions that are already in widespread use, and in keeping with precedent in other neonatal studies. Verbal consent is well received by parents and clinicians and has been used in other RCT evaluating interventions that are already in wide use, including the current NIHR funded clinical trial of a medicinal product, BASE (ISRCTN 18260410, REC Ref 23/EM/0244, IRAS ID 1007672).

Verbal consent will be documented via the eCRF (source) by the member of the clinical care team who has explained the study and sought consent. The consent discussion will be documented in the medical notes including the version of the PIS given, including that both Part 1 and 2 were given, the date of consent and name of the staff member having the discussion and taking consent. If there are issues with accessing the eCRF, the COLLABORATE verbal consent statement will be used to record consent. a printed copy of the completed electronic verbal statement or a copy of the paper statement will be provided to participants.

Cot cards and labels for paper based medical records will be provided to remind clinical staff and parents about the study while in the neonatal unit. There will also be posters available with QR codes for links to the study website and information videos.

Before discharge from the neonatal unit, a discussion will take place with parents to remind them that they will be contacted at 2 years to ask them to complete the PARCA-R questionnaire. Parents will be asked to confirm their contact details at discharge.

Written informed consent by the babies parent/legal guardian will be taken for participants taking part in the mechanistic sub-study.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

☐ Yes ☒ No

If No, how will it be recorded?

Written informed consent by the babies parent/legal guardian will only be sought for participants taking part in the mechanistic sub-study.

Verbal consent will be taken for the randomised aspects of the study.

A31. How long will you allow potential participants to decide whether or not to take part?

The first randomised intervention will be initiated when the attending clinician determines a supplemental feed is required and the second when the baby is receiving 60-120ml/kg/day human milk. Hence parents will be approached following their baby's neonatal unit admission at a time thought appropriate clinically and mindful of the desire to give them as much time as possible to decide.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- ☒ Yes
- ☐ No
- ☐ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

As the interventions are all in widespread use, co-enrolment of infants is appropriate and not precluded.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

The parent information sheet and consent form will be available in English, Welsh and the ten other most prevalent UK languages (Polish; Romanian; Punjabi; Urdu; Portuguese; Spanish; Arabic; Bengali; Gujarati; Italian).

Local interpreters arranged through the NHS sites will also be available where required.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Parent information sheet and consent form will be available in Welsh.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

All interventions are routinely used in clinical care. If new information does become available, this will be considered by the Trial Steering Committee (TSC) who will advise on making this available to local investigators and participant parents.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

- ☐ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ☐ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ☐ The participant would continue to be included in the study.
- ☐ Not applicable – informed consent will not be sought from any participants in this research.
- ☒ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

All interventions are routinely used in clinical care so the participant would remain in the trial in the unlikely event that a sole or both parents/legal guardians lost capacity. It is not possible for the research team to monitor consent after the participant is discharged, prior to the 2 year outcome.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential

participants)?(Tick as appropriate)

- ☒ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☒ Electronic transfer by magnetic or optical media, email or computer networks
- ☒ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☒ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☒ Storage of personal data on any of the following:
 - ☐ Manual files (includes paper or film)
 - ☒ NHS computers
 - ☐ Social Care Service computers
 - ☐ Home or other personal computers
 - ☒ University computers
 - ☐ Private company computers
 - ☒ Laptop computers

Further details:

Medical records (which include personal addresses, postcodes, telephone numbers) will be accessed by members of the study team or regulators for the purposes of monitoring and audit/inspection, this is outlined within the Parent Information Sheet and will be explained as part of the consent process.

Clinical data on all babies enrolled in the study, extracted from their National Neonatal Research Database record and a trial specific database (OpenClinica V4.0) will be held at Imperial Clinical Trials Unit pseudonymised with a Trial ID.

Access to personal identifiable data in the NNRD will be limited to the Chief Investigator and NNRD Data Analyst. No identifiers are permitted to be held on laptop computers.

Laptop computers may be used by University staff due to hybrid working.

Personal emails or telephone numbers will be used to prompt participants to complete the electronic PARCA-R questionnaire at 2 years. NHS number will be collected for access to long term outcomes from NHS Digital or similar organisations. Consent will be explicitly sought for this. Consent will also be sought to contact participants in the future.

A37. Please describe the physical security arrangements for storage of personal data during the study?

The NHS Code of Confidentiality will be followed by all research staff. They are aware of confidentiality of personal data and meeting the requirements of the General Data Protection Regulations. All personal identifying data will be kept on NHS computers with appropriate safeguards, eg. passwords and restricted access by research staff. Any paper or electronic files will be stored securely at participating NHS Trusts, with access restricted to authorised personnel.

The majority of trial data will be collected through the NNRD. To summarise, clinical data is extracted from Electronic Patient Records (EPR) and sent to the NNRD team where following quality-assurance and curation, data are entered into the NNRD. the All data held NNRD is de-identified. NNRD data will be stored in two locations. Upon arrival from the EPR system supplier, data are split into:

- Data items that contain dates and times
- Pseudo-anonymised data

Data items that contain dates and times are stored on a password protected NHS server at Chelsea and Westminster Hospital. Access to this NHS server is restricted to the Senior Data Analyst and one other Data Analyst. The remaining

pseudo-anonymised data are securely transferred to a Imperial College London server. This server is based within the Imperial Data Centre, is password protected and access is restricted to NNRD Analysts only and the Chief Investigator.

Data for COLLABORATE

COLLABORATE-specific trial data will be obtained in two ways; i) as an extraction from the NNRD; and ii) through the electronic Case Report Form (eCRF), OpenClinica. Trial data will be stored at the Imperial Clinical Trials Unit (ICTU). Identifiable NNRD data will be transferred from the NHS server at Chelsea and Westminster to ICTU using a secure transfer service. Access to this NHS server is restricted to the Senior Data Analyst and one other Data Analyst.

The trial eCRF will be accessed online by the researchers and trial management team at ICTU; this will contain trial data (including NHS number) from which data reports can be downloaded for data management and monitoring purposes. The trial databases are user restricted and account logins are password protected with multi-factor authentication. NHS number will be held in a secure location with restricted access. Unique codes that could allow linking of the data to identify participants, are kept securely on a separate NHS computer.

Paper trial documents will be stored in a locked cupboard at ICTU.

Electronic PARCA-r data:

As part of COLLABORATE, an electronic method for recording of PARCA-r data will be provided. This will be completed online using OpenClinica but held separately to the COLLABORATE specific dataset. Research teams will be able to use the same link and login to access this eCRF. This data will be extracted and combined with the NNRD dataset and the COLLABORATE data set at ICTU for analysis. This data will also be transferred securely to the data analyst team for inclusion in the NNRD.

A dataflow diagram will be implemented to ensure clarity of data transfer between systems.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Data will be collected according to the Data Protection Act 2018 and in line with General Data Protection Regulations. The majority of trial data will be obtained from the National Neonatal Research Database (NNRD), an established research database. COLLABORATE specific data will be extracted and held on a server at ICTU. All analysis will be undertaken on de-identified data. NNRD data may be linked to the COLLABORATE pseudonymised trial data by a unique code, the "Badger ID".

Confidentiality will be maintained through the use of dedicated Trial ID numbers.

The NHS Code of Confidentiality will be followed by all research staff. They are aware of confidentiality of personal data and meeting the requirements of the General Data Protection Regulations.

Long term storage of trial data will be at ICTU.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Research staff at each study site will have access to participants' personal data.

The Trial Manager/Monitor from Imperial Clinical Trials Unit will have access to view personal records for monitoring purposes (source-data verification, eligibility and existence verification) during monitoring visits, on the participating site premises and at NNRD. The Sponsor (Research Governance and Integrity Team) or other potential participating site NHS R&D offices and other regulatory bodies will also have the above access if conducting an audit or inspection of this study. The parent information sheet (PIS) explains that 'people will use this information to do the research or to check your baby's records to make sure that the research is being done properly.'

Limited personal information will be shared with the study team in order to provide reminders for the questionnaire at 2 years and to provide updates on the trial and results dissemination. NHS/CHI/H&C number will be collected to access long term outcomes from NHS Digital or similar organisations. Consent will be sought for this. This data will be held securely in OpenClinica with limited personnel having access, only where required to perform the tasks.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Only researchers involved in the study will undertake analysis of data, specifically the senior and study statisticians assigned to the study, from Imperial Clinical Trials Unit, Imperial College London. A pseudonymised complete dataset from the electronic data capture system (trial database OpenClinica 4.0) will be downloaded/processed by Imperial College London ICT and provided to the study statistician for analysis purposes. A dataset from the NNRD will be provided alongside to the study statistician.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title Forename/Initials Surname
	Prof Victoria Cornelius
Post	Professor of Medical Statistics and Trial Methodology, Director of the Imperial Clinical Trials Unit
Qualifications	BSc; PhD
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Post Code	W12 7RH
Work Email	v.cornelius@imperial.ac.uk
Work Telephone	0207 594 3445
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- ☐ Less than 3 months
☐ 3 – 6 months
☐ 6 – 12 months
☐ 12 months – 3 years
☒ Over 3 years

If longer than 12 months, please justify:

The trial data set will be held at Imperial College London for 10 years as per sponsor policy.

A44. For how long will you store research data generated by the study?

Years: 10

Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The trial research data will be stored at ICTU and subsequently archived in accordance with Imperial College London Standard operating procedures.

Access to de-identified trial data will be granted to appropriate organisations following applications to the COLLABORATE trial management group.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

☒ Yes ☐ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined. Participants taking part in the mechanistic sub-study will receive travel reimbursements and a thank you token (£20 shopping voucher).

There are no additional visits for participants in the main COLLABORATE study so no reimbursement is required.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

☐ Yes ☒ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

☐ Yes ☒ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

☒ Yes ☐ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

☒ Yes ☐ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

☒ Yes ☐ No

Please give details, or justify if not registering the research.
Registration with ISRCTN

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- ☒ Peer reviewed scientific journals
- ☐ Internal report
- ☒ Conference presentation
- ☒ Publication on website
- ☒ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

Results will be shared with NHS clinicians, commissioners, managers and policymakers, professional organisations, charities, and patient groups through academic and lay publications, conferences, workshops, social media, and strong personal networks. We are in regular communication with every neonatal unit in the UK as they all contribute to the NNRD, providing us with additional means of providing information directly.

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Data will be presented in aggregate form, this will ensure that anonymity is maintained.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.

We will produce a variety of outputs in varying formats to explain and disseminate results once available. Formats will include lay publications, and presentations at workshops and on social media channels (e.g., YouTube; BlueSky; Facebook; Linked-In). We will produce multimedia outputs including video animations, infographics, neonatal unit posters, and use state-of-the-art methods such as software to create short, easily comprehensible summaries of results and their implications spoken by Artificial Intelligence generated avatars in multiple languages.

Participant's parents/legal guardians will be notified of study results at two time points; first upon publication of outcomes to neonatal unit discharge, and second, upon publication of age two-year outcomes.

We will be assisted in dissemination by collaborators and partners.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- ☒ Independent external review
- ☐ Review within a company
- ☒ Review within a multi-centre research group
- ☒ Review within the Chief Investigator's institution or host organisation
- ☒ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The COLLABORATE study was peer reviewed by the funder (NIHR) as part of the application process as well as by the ICTU Collaborations Committee as part of the ICTU collaboration process. The study has also been reviewed by all collaborators involved.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- ☒ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☒ Review by a statistician within the Chief Investigator's institution
- ☒ Review by a statistician within the research team or multi-centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

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	Prof Victoria Cornelius
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E-mail	v.cornelius@imperial.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Survival to 34 weeks postmenstrual age without surgical NEC

A58. What are the secondary outcome measures?(if any)

Secondary

Assessed at 34 weeks postmenstrual age

- Survival
- Surgical NEC

• Spontaneous Intestinal Perforation

Assessed at 36 weeks postmenstrual age

- Bronchopulmonary dysplasia

Assessed at postnatal age 28 days

- Survival

Assessed at neonatal unit discharge (or death)

- Survival
- Surgery for NEC or NEC related condition after 34 weeks postmenstrual age
- Medical NEC

- Age in days to achieve an enteral intake of 150 ml/kg/day
- Treated retinopathy of prematurity
- Severe brain injury
- Any diagnosis of milk-curd obstruction
- Length of neonatal unit stay
- Number of episodes of bacterial or fungal bloodstream infection
- Number of episodes of bacterial or fungal cerebrospinal fluid infection
- Number of episodes of bacterial or fungal urinary tract infection
- Number of days of antibiotic treatment
- Number of days on parenteral nutrition
- Number of days nil by mouth
- Weight, length, and head circumference Z-scores
- Change from birth in Z-scores for weight, length, and head circumference
- Any breast feeding (suckling at breast)
- Exclusive breast feeding (suckling at breast)
- Receiving any expressed Own Mother's Milk
- Receiving exclusive expressed Own Mother's Milk
- Maximum serum urea, creatine, and alkaline phosphatase
- Health resource use
- Assessed at neonatal unit discharge (or death) in babies with NEC surgery
- Drain insertion prior to surgery (yes/no)
- Diagnosis of short bowel syndrome (yes/no)
- Diagnosis of intestinal failure-associated liver disease (yes/no)
- Length of bowel resected (cm)
- Primary surgical procedure (ileostomy; colostomy; end-to-end anastomosis)
- Number of re-operations (excluding primary operation)
- Assessed at age 2-years corrected for prematurity
- Survival without moderate-severe cognitive-language impairment
- Survival
- Moderate-severe cognitive-language impairment
- Cognitive sub-score
- Language sub-score
- Gross motor function
- Hearing impairment
- Vision impairment

Tertiary

Assessed at term-equivalent age (38-42 weeks postmenstrual age)

- Cerebral white matter microstructure indexed by fractional anisotropy values using tract-based spatial statistics

Assessed at neonatal unit discharge (or death)

- In-hospital healthcare costs

Assessed at age two-years (corrected for prematurity)

- Healthcare costs (subject to additional funding)

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 3252

Total international sample size (including UK): 3252

Total in European Economic Area: 3252

Further details:

As this is an adaptive trial, the sample size is not fixed. The maximum sample size is 3252, assuming no early stopping and a 50% co-enrolment rate. If co-enrolment is higher the number of individual babies randomised will be lower.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

The maximum sample size is 3252, (n=2168 in each randomisation; n=1084 per arm) assuming no early stopping, estimated on the composite primary efficacy outcome (survival to 34 weeks gestational age without surgical NEC (Y/N)) which, and based on the following assumptions:

- MCID of 0.05 (from 0.87 to 0.82) in the proportion "survival to 34 weeks gestation without surgical NEC" (primary

outcome); we have accurately estimated the baseline 0.82 from the National Neonatal Research Database for this population of babies in the UK

- 2-sided alpha of 0.05
- three planned looks at the data (at 50%, 75%, and 100% recruitment)
- maximum 2% withdrawal rate of consent to use NNRD data
- 50% co-enrolment rate

Based on these assumptions, recruitment of n=3252 unique participants in total will provide a minimum of 87% power for each randomisation. If co-enrolment is higher, power will increase. The expected sample size across both randomisations is n=2439.

Mechanistic sub-study: Based on computational modelling and prior precedent from neonatal neuroprotection trials, a study of 60 infants in each treatment group will enable detection of a 10% difference in fractional anisotropy with 80% power, 2-sided 5% significance.

A61. Will participants be allocated to groups at random?

☒ Yes ☐ No

If yes, please give details of the intended method of randomisation:

The study involves two randomisations. Babies may participate in either or both randomisations.

Randomisation will be carried out electronically using an on-line Electronic Data Capture system managed by the ICTU Clinical Data Systems Team. We will use minimisation (with 10% random allocation) to achieve balance between the number of babies in each treatment group over important, well-recognised prognostic factors [Neonatal Network (N=13); gestational age category (<26w; >=26w); severe growth restriction (<10% centile; >=10% centile based on standard criteria)]. Multiple births will be randomised individually in keeping with our feasibility study, other feeding trials, and parent focus group advice.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

We will construct a detailed statistical analysis plan, signed off by the Chief Investigators and Trial Steering Committee prior to the first interim analysis. We will summarise baseline characteristics by randomisation arm within each comparison using appropriate statistical measures (mean, standard deviation; median, interquartile range; frequencies; percentages). The flow of participants through both comparisons will be reported according to the CONSORT Extension for Adaptive Designs. We will target a treatment policy estimand to estimate the effect of each intervention as delivered in practice regardless of any events that occur post-randomisation. The efficacy and safety analyses for both randomisations will be based on the intention-to-treat population.

Primary end point: The study has been powered separately for the two clinical research questions (randomisations), based on around 50% co-enrolment. We will model the main intervention effect for each randomisation separately. For both, we will use a binomial Generalized Estimating Equation (GEE) model with identity link and a log link function to estimate adjusted risk difference and adjusted risk ratio (in line with CONSORT reporting recommendations) with robust variance

Interim assessment of efficacy: We will conduct two pre-planned formal interim efficacy analyses when 50% and 75% of participants reach 34 weeks gestational age. The analysis will employ two-sided O'Brien-Fleming efficacy boundaries. Adjusted between arm differences in proportions will be calculated using the primary analysis models described for the final analysis. An identity link function will be used to obtain adjusted risk differences and corresponding Z-scores. Superiority will be assessed at each stage based on the critical value thresholds (Z-scores) and numbers of participants.

Safety analyses: We will tabulate adverse events by intervention arms for each randomisation. For safety events of special interest (death, sepsis, surgical NEC, medical NEC, and other components of the neonatal and NEC core outcome sets) we will follow the principle of the primary analysis

Mechanistic sub-study: We will use Tract-based Spatial Statistics (TBSS) for analyses

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

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	Prof Victoria Cornelius
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	Title Forename/Initials Surname
	Dr Sabita Uthaya
Post	Consultant Neonatologist; Professor of Practice
Qualifications	MBBS, MD
Employer	Imperial College London
Work Address	Neonatal Unit, 3rd Floor, Chelsea and Westminster Hospital, Chelsea and Westminster Campus, 369 Fulham Rd London
Post Code	SW10 9NH
Telephone	02033158000
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	Title Forename/Initials Surname
	Prof James Boardman
Post	Professor of Neonatal Medicine
Qualifications	PhD, MSc, MBBS, BSc, Member RCPCH
Employer	The University of Edinburgh
Work Address	Centre for Clinical Brain Sciences Chancellor's Building, 49 Little France Crescent Edinburgh
Post Code	EH16 4SB
Telephone	01312422567
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Work Email	james.boardman@ed.ac.uk

	Title Forename/Initials Surname
	Prof Shalini Ojha
Post	Professor of Neonatal Medicine
Qualifications	PhD, Medical Education Diploma, MD, MBBS, Member - MRCPCH

Employer The University of Nottingham
 Work Address Faculty of Medicine & Health Sciences
 Queen's Medical Centre, Lenton
 Nottingham
 Post Code NG7 2HA
 Telephone 01159515151
 Fax
 Mobile
 Work Email shalini.ojha@nottingham.ac.uk

Title Forename/Initials Surname
 Dr Sze Ying (Hilary) Wong
 Post Consultant; Affiliated Assistant Professor
 Qualifications MB ChB, MSc, PHD, MA
 Employer University of Cambridge
 Work Address Department of Paediatrics

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Title Forename/Initials Surname
 Dr David Quine
 Post Consultant in Neonatal Medicine
 Qualifications MD, MB ChB, BSc, Member - RCPCH
 Employer NHS Lothian
 Work Address Edinburgh Royal Infirmary
 51 Little France Crescent, Old Dalkeith Rd,
 Edinburgh
 Post Code EH16 4SA
 Telephone
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 Mobile 07728966304
 Work Email david.quine@nhslothian.scot.nhs.uk

Title Forename/Initials Surname
 Prof John Norrie
 Post Director ECTU, Professor of Medical Statistics
 Qualifications BSc, MSc
 Employer The University of Edinburgh
 Work Address Edinburgh Clinical Trials Unit (ECTU)
 Usher Building, 5-7 Little France Road, Edinburgh BioQuarter - Gate 3
 Edinburgh
 Post Code EH16 4UX
 Telephone 01316517895
 Fax
 Mobile

Work Email j.norrie@ed.ac.uk

Title Forename/Initials Surname
Prof James Wason

Post Professor of Biostatistics

Qualifications BA, MPhil, PhD

Employer University of Newcastle

Work Address Population Health Sciences Institute

Baddiley-Clark Bldg

Newcastle upon Tyne

Post Code NE2 4AX

Telephone

Fax

Mobile 07905676991

Work Email james.wason@newcastle.ac.uk

Title Forename/Initials Surname
Dr Ramon Luengo- Fernandez

Post Associate Professor of Health Economics

Qualifications D Phil, MSc, MA

Employer National Perinatal Epidemiology Unit

Work Address Health Economics, Old Road Campus

Headington

Oxford

Post Code Ox3 7LF

Telephone 01865289264

Fax

Mobile

Work Email ramon.luengo-fernandez@dph.ox.ac.uk

Title Forename/Initials Surname
Dr Annemarie Lodder

Post Parent, Patient and Public Involvement and Engagement Lead

Qualifications PhD, MSc, BSc

Employer Imperial College London

Work Address School of Public Health

Post Code

Telephone

Fax

Mobile 07805416103

Work Email a.lodder@imperial.ac.uk

Title Forename/Initials Surname
Prof Andrew Morris

Post Director

Qualifications Mb ChB, MD, MSc

Employer Health Data Research UK

Work Address Health Data Research

Post Code

Telephone

Fax

Mobile 07976535328

Work Email andrew.morris@hdruk.ac.uk

Title Forename/Initials Surname

Ms Lauren Ingledow

Post Founder

Qualifications

Employer Adult Preemie Advocacy Network

Work Address 30 Meadow Lane
Newmarket

Post Code CB8 8FZ

Telephone

Fax

Mobile 07587091354

Work Email lingledow@hotmail.com

Title Forename/Initials Surname

Mr Peter Bradley

Post Director of Services

Qualifications

Employer Bliss

Work Address 10-18 Union Street
London

Post Code SE1 1SZ

Telephone

Fax

Mobile 07921920358

Work Email peterbradley@bliss.org.uk

Title Forename/Initials Surname

Dr Daphne Babalis

Post Director of Operations

Qualifications PhD

Employer Imperial College London

Work Address Imperial Clinical Trials Unit, 1st Floor Stadium House
68 Wood Lane
London

Post Code W12 7RH

Telephone 0207 594 3403

Fax

Mobile 07714 051 465

Work Email d.babalis09@imperial.ac.uk

A64. Details of research sponsor(s)**A64-1. Sponsor****Lead Sponsor**Status: ☐ NHS or HSC care organisation☒ Academic☐ Pharmaceutical industry☐ Medical device industry☐ Local Authority☐ Other social care provider (including voluntary sector or private organisation)☐ OtherCommercial status: ☐ Non-Commercial*If Other, please specify:***Contact person**

Name of organisation Imperial College London

Given name Ruth

Family name Nicholson

Address Research Governance and Integrity Team, Imperial College London and Imperial College Healthcare NHS

Town/city London

Post code W2 1PG

Country United Kingdom

Telephone 0207 594 9480

Fax

E-mail r.nicholson@imperial.ac.uk

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)*Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU***Contact person**

Name of organisation

Given name

Family name

Address

Town/city

Post code

Country

Telephone

Fax
E-mail

A65. Has external funding for the research been secured?*Please tick at least one check box.*

- ☒ Funding secured from one or more funders
☐ External funding application to one or more funders in progress
☐ No application for external funding will be made

What type of research project is this?

- ☒ Standalone project
☐ Project that is part of a programme grant
☐ Project that is part of a Centre grant
☐ Project that is part of a fellowship/ personal award/ research training award
☐ Other

Other – please state:

Please give details of funding applications.

Organisation National Institute for Health and Care Research
 Address NIHR Coordinating Centre
 Alpha House, Enterprise Road
 Southampton
 Post Code S016 7NS
 Telephone
 Fax
 Mobile
 Email eme@nihr.ac.uk

Funding Application Status: ☒ Secured ☐ In progress

Amount: 2,970,558.00

Duration

Years: 5

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Efficacy and Mechanism Evaluation (EME) Programme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? Please give details of subcontractors if applicable.

☐ Yes ☒ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

☐ Yes ☒ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title Forename/Initials Surname
	Damon Foster
Organisation	Research & Development Office
Address	Chelsea and Westminster Hospital NHS Foundation Trust Unit G3. Harbour Yard, Chelsea Harbour, London
Post Code	SW10 0XD
Work Email	Damon.foster2@nhs.net
Telephone	020 3316 6887
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A68-2. Select the Regional Research Delivery Network for the NHS Organisation identified in A68-1:

North West London

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/06/2025

Planned end date: 31/05/2030

Total duration:

Years: 4 Months: 11 Days: 30

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial ⁽¹⁾

The end-of-trial is the point at which the final PARCA-R questionnaire is completed.

A71-1. Is this study?

☐ Single centre
☒ Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

- ☒ England
☒ Scotland
☒ Wales
☒ Northern Ireland
☐ Other countries in European Economic Area

Total UK sites in study 190

Does this trial involve countries outside the EU?

☐ Yes ☒ No

A72. Which organisations in the UK will host the research? Please indicate the type of organisation by ticking the box and give approximate numbers if known:

- | | |
|---|-----|
| ☒ NHS organisations in England | 159 |
| ☒ NHS organisations in Wales | 9 |
| ☒ NHS organisations in Scotland | 15 |
| ☒ HSC organisations in Northern Ireland | 7 |
| ☐ GP practices in England | |
| ☐ GP practices in Wales | |
| ☐ GP practices in Scotland | |
| ☐ GP practices in Northern Ireland | |
| ☐ Joint health and social care agencies (eg community mental health teams) | |
| ☐ Local authorities | |
| ☐ Phase 1 trial units | |
| ☐ Prison establishments | |
| ☐ Probation areas | |
| ☐ Independent (private or voluntary sector) organisations | |
| ☐ Educational establishments | |
| ☐ Independent research units | |
| ☐ Other (give details) | |

Total UK sites in study: 190

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

☐ Yes ☒ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The study will be monitored on-site periodically by trial staff to assess progress, verify adherence to the protocol, ICH GCP E6 guidelines and other national requirements and review the completeness, accuracy and consistency of the

data. Direct access will be granted to authorised representatives from trial organisers, the research Sponsor and NHS trusts to permit trial-related monitoring, audits and inspections.

This trial is a comparison of standard treatments, which does not include a medicine, so does not fall under the auspices of the MHRA. This trial poses minimal risk, no greater than normal care within a neonatal unit, to either the participants or the health care professionals delivering the trial.

Central monitoring will be used at ICTU to monitor patterns of recruitment at sites and within the data; data completeness and quality; safety reports and outliers in the clinical data will be investigated and may trigger 'for cause' site monitoring.

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

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

A Data Monitoring and Ethics Committee will operate in accordance with the Damocles Group charter and comprise 4-6 members including a PPPIE member, and a Chair with relevant previous experience, to facilitate effective interactions, and good understanding of both clinical and statistical issues. This committee will receive reports supplied in confidence and will advise the Trial Steering Committee on whether the accumulated data from the study, together with results from other relevant research, justifies continuing recruitment. The Data Monitoring and Ethics Committee will meet first during trial set-up to agree the content of the charter, at the end of the pilot phase and then at 50% and 75% recruitment.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The study may be prematurely terminated for the following reasons:

- Event/s which in the opinion of the Trial Steering Committee contraindicate further randomisation of additional participants
- Sponsor's decision
- Research Ethics Committee's decision.
- Funder's decision

An internal pilot will take place 9 months after recruitment has started. It will use traffic light system to evaluate recruitment rate, co-enrolment rate and withdrawal rate: if the red criteria are met there will be a discussion with the Trial Steering Committee about stopping the trial. The DMEC Charter will define procedures for early termination of the study due to safety, should this be required. The DMEC will also meet at 50% and 75% recruitment.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

The Sponsor has civil liability insurance, which covers this study in the United Kingdom. Imperial College London

holds negligent harm and non-negligent harm insurance policies which apply to this study. Imperial College London will act as the Sponsor for this trial.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

The Sponsor has civil liability insurance, which covers this study in the United Kingdom. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Imperial College London will act as the Sponsor for this trial.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- ☒ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

- ☒ Yes ☐ No

If Yes, please give details of the compensation policy:
Imperial College London "no-fault" indemnity for clinical studies.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

- ☐ Yes ☒ No ☐ Not sure

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Stool samples, between 7 and 14 samples depending on the gestational age

2. Who will collect the samples?

The research team at the participating sites. Samples will be collected from soiled nappies removed from participants.

3. Who will the samples be removed from?

- ☒ Living donors
☐ The deceased

4. Will informed consent be obtained from living donors for use of the samples? Please tick as appropriate

In this research?

- ☒ Yes ☐ No

In future research?

- ☒ Yes ☐ No ☐ Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

- ☐ Yes ☒ No

8. Will the samples be stored: [Tick as appropriate]

In fully anonymised form? (*link to donor broken*)

- ☐ Yes ☒ No

In linked anonymised form? (*linked to stored tissue but donor not identifiable to researchers*)

- ☒ Yes ☐ No

If Yes, say who will have access to the code and personal information about the donor.

All samples will be identified by a Trial ID. The link to the identifiable data will be held at the participating site.

In a form in which the donor could be identifiable to researchers?

- ☐ Yes ☒ No

9. What types of test or analysis will be carried out on the samples?

DNA analysis of the bacteria in stool samples to identify if different feeding methods results in a different gut microbiota composition and/or diversity, exploring mechanisms linking nutritional exposures to brain development through gut-brain interactions,

10. Will the research involve the analysis or use of human DNA in the samples?

- ☐ Yes ☒ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

☐ Yes ☒ No

12. If so, will arrangements be made to notify the individuals concerned?

☐ Yes ☐ No ☒ Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Samples will be processed and stored at -80°C in the Centre for Reproductive Health at the University of Edinburgh under a HTA licence for later analyses. All samples will be stored with anonymised sample IDs and Trial IDs. All samples will be fully tracked with complete chain of custody when transported.

14. What will happen to the samples at the end of the research? Please tick all that apply and give further details.

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☒ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☒ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☒ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

Any remaining samples at the end of the project will be stored by research team pending ethical approval for use in another project. The samples may also be stored by the research team where they are "non relevant material". If a negligible volume of sample remains, they will be disposed of in accordance with the Human Tissue Authority's Code of Practice.

PART B: Section 7 - Children**1. Please specify the potential age range of children under 16 who will be included and give reasons for carrying out the research in this age group.**

The study will include babies born <29 weeks gestation up to age 2 years. The study aim is to determine the safety of widely used enteral feeds in reducing necrotising enterocolitis, mortality, and cognitive impairment in extremely preterm babies. The condition that the study is trying to prevent, necrotising enterocolitis, occurs predominantly in preterm infants

2. Indicate whether any children under 16 will be recruited as controls and give further details.

The study is a randomised trial so recruited infants (less than 29 weeks gestation) will be randomly assigned (with an equal chance) to one of two study arms in either randomisation. All 4 arms represent current clinical practice in the UK.

3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

Parents/legal guardians will give consent on behalf of their babies. Child assent is not appropriate due to the age of the participants (2 years adjusted for prematurity at the end of their participation).

4. If you intend to provide children under 16 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.

Not applicable

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For further information please refer to guidance.

Investigator identifier	Research site	Investigator Name
IN1	☒ NHS/HSC Site ☐ Non-NHS/HSC Site	Forename Luke Middle name Family name Mills Email luke.mills3@nhs.net Qualification (MD...) Country United Kingdom
	Organisation name CHELSEA AND WESTMINSTER HOSPITAL NHS FOUNDATION TRUST Address CHELSEA & WESTMINSTER HOSPITAL 369 FULHAM ROAD LONDON Post Code SW10 9NH Country ENGLAND	
IN2	☒ NHS/HSC Site ☐ Non-NHS/HSC Site	Forename David Middle name Family name Quine Email David.Quine@nhs.scot Qualification (MD...) Country United Kingdom
	Organisation name LOTHIAN Address WAVERLEYGATE 2-4 WATERLOO PLACE EDINBURGH CITY OF EDINBURGH Post Code EH1 3EG Country SCOTLAND	
IN3	☒ NHS/HSC Site ☐ Non-NHS/HSC Site	Forename Catriona Middle name Family name Macdougall Email catriona.macdougall@nhs.net Qualification (MD...) Country
	Organisation CAMBRIDGE UNIVERSITY HOSPITALS	

	name	NHS FOUNDATION TRUST	Country	United Kingdom
	Address	CAMBRIDGE BIOMEDICAL CAMPUS HILLS ROAD CAMBRIDGE		
	Post Code	CB2 0QQ		
	Country	ENGLAND		
IN4	☒ NHS/HSC Site ☐ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Shalini Ojha Shalini.Ojha@nottingham.ac.uk United Kingdom
	Organisation name	UNIVERSITY HOSPITALS OF DERBY AND BURTON NHS FOUNDATION TRUST		
	Address	ROYAL DERBY HOSPITAL UTTOXETER ROAD DERBY		
	Post Code	DE22 3NE		
	Country	ENGLAND		
IN5	☒ NHS/HSC Site ☐ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Sanjeev Deshpande sanjeev.deshpande@nhs.net United Kingdom
	Organisation name	THE SHREWSBURY AND TELFORD HOSPITAL NHS TRUST		
	Address	MYTTON OAK ROAD SHREWSBURY		
	Post Code	SY3 8XQ		
	Country	ENGLAND		
IN6	☒ NHS/HSC Site ☐ Non-NHS/HSC Site		Forename Middle name Family name Email	Fergus Harnden Fergus.Harnden@belfasttrust.hscni.net

Organisation name	BELFAST HEALTH AND SOCIAL CARE TRUST	Qualification (MD...)	
Address	TRUST HEADQUARTERS A FLOOR - BELFAST CITY HOSPITAL LISBURN ROAD BELFAST	Country	United Kingdom
Post Code	BT9 7AB		
Country	NORTHERN IRELAND		

IN7

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename	Sanjeev
Middle name	
Family name	Bali
Email	sanjeev.bali@northerntrust.hscni.net

Organisation name	NORTHERN HEALTH AND SOCIAL CARE TRUST	Qualification (MD...)	
Address	TRUST HEADQUARTERS BRETEN HALL BUSH ROAD ANTRIM COUNTY ANTRIM	Country	United Kingdom
Post Code	BT41 2RL		
Country	NORTHERN IRELAND		

IN8

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename	Nita
Middle name	
Family name	Saxeena
Email	Nita.Saxena@setrust.hscni.net

Organisation name	SOUTH EASTERN HEALTH AND SOCIAL CARE TRUST	Qualification (MD...)	
Address	TRUST HEADQUARTERS ULSTER HOSPITAL UPPER NEWTOWNARDS ROAD DUNDONALD BELFAST COUNTY DOWN	Country	United Kingdom
Post Code	BT16 1RH		
Country	NORTHERN IRELAND		

IN9

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Damien

Middle
nameFamily
name ArmstrongOrganisation
name WESTERN HEALTH AND
SOCIAL CARE TRUST

Email Damien.Armstrong@westerntrust.hscni.net

Address MDEC BUILDING
ALTNAGELVIN AREA
HOSPITAL SITE
GLENSHANE ROAD
LONDONDERRY
COUNTY
LONDONDERRYQualification
(MD...)

Country United Kingdom

Post Code BT47 6SB

Country NORTHERN IRELAND

IN10

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Alison

Middle name

Family name Verner

Email alison.verner@southerntrust.hscni.net

Organisation
name SOUTHERN HEALTH
AND SOCIAL CARE
TRUSTQualification
(MD...)

Country United Kingdom

Address SOUTHERN AREA
COLLEGE OF NURSING
CRAIGAVON AREA
HOSPITAL
68 LURGAN ROAD,
PORTADOWN
CRAIGAVON COUNTY
ARMAGH

Post Code BT63 5QQ

Country NORTHERN IRELAND

IN11

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Joe

Middle name

Family name Fawke

Email Joe.fawke@uhl-tr.nhs.uk

Organisation
name UNIVERSITY HOSPITALS
OF LEICESTER NHS
TRUSTQualification
(MD...)

Country United Kingdom

Address LEICESTER ROYAL
INFIRMARY
INFIRMARY SQUARE
LEICESTER

	Post Code	LE1 5WW		
	Country	ENGLAND		
IN13	☒ NHS/HSC Site		Forename	Vimal
	☐ Non-NHS/HSC Site		Middle name	
			Family name	Vasu
			Email	vimal.vasu@nhs.net
	Organisation name	EAST KENT HOSPITALS UNIVERSITY NHS FOUNDATION TRUST	Qualification (MD...)	
	Address	KENT & CANTERBURY HOSPITAL ETHELBERT ROAD CANTERBURY	Country	United Kingdom
	Post Code	CT1 3NG		
	Country	ENGLAND		

PART D: Declarations**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.
3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.
10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
 - ◊ Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
 - ◊ May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
 - ◊ May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
 - ◊ Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - ◊ May be sent by email to REC members.
11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.
12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ☐ Chief Investigator
- ☐ Sponsor
- ☐ Study co-ordinator
- ☐ Student
- ☐ Other – please give details
- ☐ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Neena Modi on 26/08/2025 08:55.

Job Title/Post: Professor of Neonatal Medicine
Organisation: Imperial College London
Email: n.modi@imperial.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

Please note: The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Miss Ruth Nicholson on 26/08/2025 08:26.

Job Title/Post: Head of Research Governance and Integrity
Organisation: Imperial College London
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