ISRCTN10443084 https://doi.org/10.1186/ISRCTN10443084

A UK-wide study to find out which routine top-up feeds for extremely preterm babies when there is insufficient own mother's milk, reduce the likelihood of necrotising enterocolitis and improve survival and brain development

Submission date 15/12/2025	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 13/01/2026	**Overall study status** Ongoing	
Last Edited 07/10/2026	**Condition category** Neonatal Diseases	

Plain English summary of protocol

Background and study aims
This study will address two uncertainties in the care of babies born less that 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.

Who can participate?
Preterm babies born below 29 weeks gestation

What does the study involve?
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). There will be no research-related procedures except for infants participating in the sub-study, who will be invited for a brain MRI at at term equivalent age (38-42 weeks) 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 as a component of routine clinical care. A digital option for completion will be provided.

What are the possible benefits and risks of participating?
The decision of which option each baby will receive will be made fairly and equally by randomisation. All feeding options used in this study are already used in UK hospitals.
If your baby takes part, they may not directly benefit themselves, but will help improve the care of preterm babies in the future. However, participants in randomised studies like COLLABORATE often have better outcomes than equivalent patients who do not take part; this is called "inclusion benefit".

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
Recruitment is planned from December 2025 to November 2027. The study will complete in May 2030.

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
1. Trial Manager, collaborate@imperial.ac.uk
2. Prof. Neena Modi, n.modi@imperial.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Prof Neena Modi

ORCID ID
https://orcid.org/0000-0002-2093-0681

Contact details
Imperial College London
Section of Neonatal Medicine
Chelsea and Westminster Hospital Campus
School of Public Health
369 Fulham Road
London
United Kingdom
SW10 9NH
-
n.modi@imperial.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
337660

Central Portfolio Management System (CPMS)
59907

National Institute for Health and Care Research (NIHR)
163188

Study information

Scientific Title
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

Acronym
COLLABORATE

Study objectives
Primary objectives:
1. To assess, in babies born <29 weeks gestation, the efficacy of pHDM compared with Preterm Formula when used as a supplement should there be insufficient milk from their own mother (Own Mother's Milk) on “survival to 34 weeks postmenstrual age without surgical NEC”
2. To assess, in babies born <29 weeks gestation, if routine cow-milk-based protein-carbohydrate fortification of human milk feeds (Own Mother’s Milk and pHDM) compared with no routine fortification, affects “survival to 34 weeks postmenstrual age without surgical NEC”

Secondary objectives:
1. To assess the efficacy of pHDM compared with Preterm Formula on language and cognitive development at age 2-years, and other outcomes in babies born <29 weeks gestation, when used as a supplement should there be insufficient milk from their own mother (Own Mother's Milk)
2. To assess if routine cow-milk-based protein-carbohydrate fortification of human milk feeds (Own Mother’s Milk and pHDM) in babies born <29 weeks gestation affects language and cognitive development at age 2-years, and other outcomes

Tertiary objectives:
1. To determine if pHDM and Preterm Formula exert different effects on neurodevelopment through the mechanism of altered cerebral white matter microstructure.
2. To establish if the additional cost of pHDM to the NHS is justified through a reduction in NEC
3. To establish if the additional cost of fortifier generates savings through improved survival to age 2 years corrected for prematurity without moderate-severe cognitive-language impairment
4. To collect and store faecal samples from participants recruited in Edinburgh who are enrolled in randomisation 1, for future mechanistic studies, subject to funding

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/10/2025, London - Bloomsbury Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; bloomsbury.rec@hra.nhs.uk), ref: 25/LO/0697

Primary study design
Interventional

Study design
Adaptive two-randomization controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Necrotising enterocolitis, mortality, and cognitive impairment in preterm babies born below 29 weeks gestation

Interventions
All interventions and comparators being used in the COLLABORATE trial are currently used as part of routine care in hospitals; no experimental treatments are being tested.

The intervention for randomisation 1 is pasteurised Human Donor Milk (pHDM) when a supplement is needed should there be insufficient milk from their own mother (Own Mother's Milk). Hospitals obtain pHDM from one of 15 human milk banks in the country that operate on a charitable or not-for-profit basis.

The intervention for randomisation 2 is multicomponent fortifier, a commercial product available as a powder added to human milk (Own Mother’s Milk and pHDM), that is prepared from cow milk and contains protein, carbohydrate, minerals, vitamins, and trace elements. Fortifiers used in the UK are standard hospital stock.

The comparator for randomisation 1 is preterm formula (standard hospital stock) when a supplement is needed should there be insufficient milk from their own mother (Own Mother's Milk).

Intervention Type
Other

Primary outcome(s)
Survival at 34 weeks postmenstrual age without surgical NEC, assessed from data held in the UK National Neonatal Research Database

Key secondary outcome(s)
All outcomes are assessed from data held in the UK National Neonatal Research Database unless otherwise stated.

The following outcomes are assessed at 34 weeks postmenstrual age:
1. Survival
2. Surgical NEC
3. Spontaneous Intestinal Perforation

The following outcomes are assessed at 36 weeks postmenstrual age:
1. Bronchopulmonary dysplasia

The following outcomes are assessed at postnatal age 28 days:
1. Survival

The following outcomes are assessed at neonatal unit discharge (or death):
1. Survival
2. Surgery for NEC or NEC-related condition after 34 weeks postmenstrual age
3. Medical NEC
4. Age in days to achieve an enteral intake of 150 ml/kg/day
5. Treated retinopathy of prematurity
6. Severe brain injury
7. Any diagnosis of milk-curd obstruction
8. Length of neonatal unit stay
9. Number of episodes of bacterial or fungal bloodstream infection
10. Number of episodes of bacterial or fungal cerebrospinal fluid infection
11. Number of episodes of bacterial or fungal urinary tract infection
12. Number of days of antibiotic treatment
13. Number of days on parenteral nutrition
14. Number of days nil by mouth
15. Weight, length, and head circumference Z-scores
16. Change from birth in Z-scores for weight, length, and head circumference
17. Any breastfeeding (suckling at breast)
18. Exclusive breastfeeding (suckling at breast)
19. Receiving any expressed Own Mother's Milk
20. Receiving exclusive expressed Own Mother's Milk
21. Maximum serum urea, creatine, and alkaline phosphatase
22. Health resource use

The following outcomes are assessed at neonatal unit discharge (or death) in babies with NEC surgery:
1. Drain insertion prior to surgery (yes/no)
2. Diagnosis of short bowel syndrome (yes/no)
3. Diagnosis of intestinal failure-associated liver disease (yes/no)
4. Length of bowel resected (cm)
5. Primary surgical procedure (ileostomy; colostomy; end-to-end anastomosis)
6. Number of re-operations (excluding primary operation)

The following outcomes are assessed using the routine PARCA-R questionnaire at age 2 years corrected for prematurity:
1. Survival without moderate-severe cognitive-language impairment
2. Survival
3. Moderate-severe cognitive-language impairment
4. Cognitive sub-score
5. Language sub-score
6. Gross motor function
7. Hearing impairment
8. Vision impairment

Tertiary outcomes:
1. Cerebral white matter microstructure indexed by fractional anisotropy values using tract-based spatial statistics from an MRI scan at term-equivalent age 37-44 weeks postmenstrual age

2. In-hospital healthcare costs are assessed at neonatal unit discharge (or death), and at age 2 years, corrected for prematurity (subject to additional funding) from data collected in the patient record

Completion date
30/01/2030

Eligibility

Key inclusion criteria
Randomisation 1:
1. Born <29 weeks gestation
2. No condition precluding enteral feeding
3. Maternal intention to express breast milk
4. The parent has provided verbal consent for the baby to participate in the trial

Randomisation 2:
1. Born <29 weeks gestation
2. No condition precluding enteral feeding
3. Maternal intention to express breast milk
4. The parent has provided verbal consent for the baby to participate in the trial

Mechanistic study:
1. Participants in randomisation 1 recruited at the Royal Infirmary of Edinburgh
2. Written informed consent for the mechanistic study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Sex
All

Total final enrolment
0

Key exclusion criteria
Randomisation 1:
1. Baby has already received pHDM, Preterm Formula

Randomisation 2:
1. Baby has already received Fortifier

Mechanistic study:
1. 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)
2. Infants with a contraindication to MRI at 3 Tesla

Date of first enrolment
19/01/2026

Date of final enrolment
30/11/2027

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
Chelsea & Westminster Hospital
369 Fulham Road
London
England
SW10 9NH

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
Scotland
EH1 3EG

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
University Hospitals of Derby and Burton NHS Foundation Trust
Royal Derby Hospital
Uttoxeter Road
Derby
England
DE22 3NE

Study participating centre
The Shrewsbury and Telford Hospital NHS Trust
Mytton Oak Road
Shrewsbury
England
SY3 8XQ

Study participating centre
Belfast Health and Social Care Trust
Trust Headquarters
A Floor - Belfast City Hospital
Lisburn Road
Belfast
England
BT9 7AB

Study participating centre
Northern Health and Social Care Trust
Antrim Area Hospital
43 Bush Road
Antrim
Northern Ireland
BT41 2QB

Study participating centre
South Eastern Health and Social Care Trust
Trust Headquarters Ulster Hospital
Upper Newtownards Road
Dundonald
Belfast
Northern Ireland
BT16 1RH

Study participating centre
Western Health and Social Care Trust
Mdec Building
Altnagelvin Area Hospital Site
Glenshane Road
Londonderry
Northern Ireland
BT47 6SB

Study participating centre
Southern Health and Social Care Trust
Southern Area College of Nursing
Craigavon Area Hospital
68 Lurgan Road, Portadown
Craigavon
Northern Ireland
BT63 5QQ

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
England
LE1 5WW

Study participating centre
East Kent Hospitals University NHS Foundation Trust
Kent & Canterbury Hospital
Ethelbert Road
Canterbury
England
CT1 3NG

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised dataset will be available as de-identified data upon request from the Chief Investigator Professor Neena Modi (n.modi@imperial.ac.uk) beginning 12 months and ending 5 years after the primary publication and pre-planned secondary analysis, following approval of a methodologically sound proposal and a signed data sharing agreement. The parent information leaflet provided to parents prior to them verbally consenting to the study explains data sharing procedures and potential future uses of study data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		06/10/2026	07/10/2026	Yes	No