COLLABORATE trial to reduce mortality, NEC and cognitive impairment in babies born below 29 weeks' gestation

We discuss COLLABORATE, a major UK-wide two-randomisation, adaptive, controlled trial to improve the care of preterm babies born below 29 weeks' gestation. COLLABORATE aims to resolve two very longstanding uncertainties: whether preterm formula or pasteurised human donor milk is the better option to make up any shortfall in the availability of own mother's milk, and whether human milk (own mother's milk and pasteurised human donor milk) requires routine fortification with protein and carbohydrate. We explain the study rationale, design and importance for patients, their families and the NHS.

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Keywords

enteral nutrition; necrotising enterocolitis (NEC); cognitive development; human donor milk; preterm formula; fortifier

Key points

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1. Non-definitive evidence suggests that preterm formula may increase the risk of necrotising enterocolitis, and pasteurised donor milk top-ups may increase the risk of neurodevelopmental impairment.
2. Routine fortification can achieve faster short-term growth, but needs more evidence to show long-term benefits.
3. Faster growth in growth restricted extremely preterm babies is a risk factor for later cardiometabolic disease.
4. Routine fortification risks providing too high an intake of protein, which is associated with adverse neuro-development and metabolic health.

What is the COLLABORATE study?

COLLABORATE is an efficient, adaptive, two-randomisation, real-world data-enabled, digital technology-facilitated, controlled trial that will tackle two very longstanding and important uncertainties in the nutritional care of preterm babies born below 29 weeks' gestation. Babies are eligible if they have no condition precluding enteral feeding and there is maternal intention to express breast milk. An integral component of COLLABORATE is to support every mother to express milk for her own baby and transition to successful breastfeeding.

The first uncertainty is whether preterm formula or pasteurised human donor milk is the better option to make up any shortfall in the availability of own mother's milk. The second is whether human milk (own mother's milk and pasteurised human donor milk) requires routine supplementation with additional protein and carbohydrate.

Randomisation one occurs when the attending clinician considers a top-up enteral feed is required because there is insufficient own mother's milk. Randomisation two occurs when the baby is receiving 60-120ml/kg of human milk.

The primary outcome is survival to 34 weeks' postmenstrual age without necrotising enterocolitis (NEC) surgery. The extensive list of secondary outcomes includes language and cognitive development at two years old, metabolic bone disease, growth and all core neonatal outcomes.[1] All outcomes are summarised in **TABLE 2**.

COLLABORATE has been approved by the UK Heath Research Authority and Health and Care Research Wales (Research Ethics Committee reference 25/LO/0697).

What other areas will COLLABORATE investigate?

COLLABORATE provides a unique opportunity to gain deeper understanding of the way in which own mother's milk, pasteurised donor milk and preterm formula impact the developing brain. A mechanistic study led by co-investigator Professor James Boardman involving sophisticated magnetic resonance brain imaging is therefore embedded in COLLABORATE. This study will only involve babies recruited in Edinburgh.

The rationale for the mechanistic study is that the third trimester of human development, which extremely preterm babies spend in a neonatal unit, is a critical period for brain development. Although major brain injury found in neonates at this period has reduced over time, neuro-impairment has not, for reasons that are unclear.[2] Around half of extremely preterm babies grow up with a neuro-impairment and feeds are a prime candidate determinant, directly through nutrient

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TABLE 1 Article co-authors. All authors contributed to designing the COLLABORATE study, obtaining funding and reviewing and approving this paper for submission.

adequacy and biologically active components in human milk, and indirectly by influencing the risk of NEC.

COLLABORATE will also include an economic analysis led at the National Perinatal Epidemiology Unit by co-investigator Professor Ramon Luengo-Fernandez. A cost-effectiveness evaluation is important given the large cost differences between pasteurised donor milk (£125-£200 per litre), preterm formula (£5 per litre), fortifier (£5/litre of human milk fortified) and the high cost of treating NEC, NEC-related co-morbidities, and neurodevelopmental impairments.

How is COLLABORATE innovative and efficient?

COLLABORATE is innovative and efficient for several reasons. It is an adaptive trial; this means the sample size is not fixed.[3] The study incorporates two pre-planned interim analyses, so that recruitment can stop as soon as answers are clear. The maximum sample size is 2,168 (1,084 per arm) for each of randomisations one and two. Babies can participate in either or both randomisations. If 50% of babies participate in both randomisations, 3,252 babies are needed to take part in total. If more than 50% babies participate in both randomisations, the total sample size will be smaller and answers will be available earlier.

The burden of data recording is minimised because most data for COLLABORATE will come from the UK National Neonatal Research Database (NNRD), to which all neonatal units in England, Scotland and Wales already contribute.[4] Northern Ireland neonatal units will submit data through a separate route. An automated, digital version of the parent report of children's abilities (PARCA-R) will be made available for participating neonatal units to use.[5] PARCA-R is a validated, NICE-recommended, parent-completed questionnaire to assess language and cognitive development at age two years corrected for preterm birth.

Who is funding and sponsoring COLLABORATE?

Collaborate is funded by the UK Department of Health through the National Institute for Health Research Efficacy and Mechanism programme. Imperial College London is the sponsor for the research and is responsible for conduct and oversight of the study.

Why is COLLABORATE important?

The questions COLLABORATE will tackle have been priority ranked by parents, parent representatives and profession al bodies in all priority setting exercises over the last 10 years.[6-8] The uncertainties affect every extremely preterm baby globally.

The NICE guidance *Donor Milk Banks: Service Operation* acknowledges the limited high-quality evidence for use of pasteurised human donor milk (pHDM) and includes the recommendation for research to evaluate efficacy in improving outcomes and identify babies who would benefit most.[9] The 2023 British Association of Perinatal Medicine *Framework for Use of Donor Milk* also highlights the urgent need for this research.[10] The Baby Friendly Initiative accepts the need for research in this area (letter to COLLABORATE investigators dated 12 September 2025) and the UK Association of Milk Banks and Neonatal Dietitians Interest Group are represented on the COLLABORATE trial steering committee.

All neonatal units aim to optimise the provision of own mother's milk for preterm babies, but in the face of a shortfall, some units use top ups of pasteurised milk and some use preterm formula. Some units routinely add extra protein and carbohydrate to human milk feeds while others do not.[11] Which option a baby receives depends on the neonatal unit where they receive care, dietetic advice or the preference of the attending clinician and not on secure evidence. Current practice is variable, confusing and dangerous for babies, because the evidence for what is optimal is very far from certain.

Necrotising enterocolitis

NEC is an acquired disease of the immature gastrointestinal tract involving bacterial invasion, sepsis and local and

Primary outcome

Assessed at 34 weeks' postmenstrual age
- Survival without surgical NEC

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
- Non-NEC or non-NEC-related surgery
- Medical NEC
- Age in days to achieve an enteral intake of 150ml/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 breastfeeding (suckling at breast)
- Exclusive breastfeeding (suckling at breast)
- Receiving any expressed own mother's milk
- Receiving exclusive expressed own mother's milk
- Maximum serum urea, creatinine 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 two 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
- Vison impairment

Tertiary

Assessed at term-equivalent age (38-42 weeks' postmenstrual age) (Edinburgh sub-study only)
- 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) (subject to additional funding)
- Healthcare costs

TABLE 1 COLLABORATE study outcomes

systemic inflammation. NEC can present subtly or devastatingly acutely, with a spectrum of severity ranging from mild to catastrophic total intestinal necrosis.[12] Parents and clinicians fear NEC, which can develop without warning. An added difficulty is that diagnosis, especially of less severe, medically-managed NEC, is imprecise and based on varying combinations of subjective clinical signs and radiological and laboratory criteria, with characteristics shared with other conditions such as preterm dysmotility and bloodstream infection-associated ileus.[13] The pathophysiology of NEC remains poorly understood and the mainstay of management is supportive, with surgery for perforated or necrotic bowel. Complications include feeding difficulties and the need for prolonged parenteral nutrition, cholestasis, liver failure, multiple episodes of systemic sepsis, growth faltering, repeated surgeries, short bowel syndrome, intestinal transplantation and brain injury.[14]

Surgical NEC is a leading cause of death and long-term impairment in preterm babies in high income countries, mainly but not exclusively affecting those born below 29 weeks' gestation. Own mother's milk reduces risk but does not eliminate the disease. In a two-year whole population study in England, 50% of babies that developed NEC requiring surgery and/or leading to death had only had human milk feeds prior to disease onset.[15] There are no other proven preventive approaches.

Probiotics have been extensively studied but no significant effects have been shown in extremely preterm infants with NEC, all-cause mortality, or late-onset invasive infection.[16]

There are around 3,000 babies born at less than 29 weeks' gestation and around 260 NEC deaths and/or surgeries each year in the UK, with up to three times more who develop disease that is less severe but nonetheless disrupts feeding, increases antibiotic exposure, prolongs hospital stay and increases healthcare costs.[15]

Why is nutritional practice so variable?

Nutritional practice is variable because of a lack of robust evidence and uncertainty around the risks and benefits of options. Some healthcare professionals fear that the use of preterm formula as a top up will increase the risk of NEC or adversely affect

breast milk expression and subsequent breastfeeding. However, others fear use of pHDM adversely affects expression and breastfeeding, especially if incorrectly regarded as equivalent to own mother's milk. There is also growing concern that use of pHDM might increase neurocognitive impairment.

Some healthcare professionals believe that extra protein and carbohydrate is always necessary to support the nutritional needs of the extremely preterm baby. However, there is also concern from emerging evidence that routine supplementation with added protein and carbohydrate increases the risk of neurodevelopmental impairment and metabolic ill health.

Some practitioners support the use of commercial fortifiers because these also contain vitamins and minerals. However, UK practice regarding mineral and vitamin supplementation is also variable. Some neonatal units have adopted highly complex guidelines that are confusing for staff and parents and increase blood tests, medications and service costs without evidence of benefit.

Preterm formula

Any formula used for babies participating in COLLABORATE will be standard NHS stock. Formula has consistent composition, is manufactured from cow milk to closely regulated quality-controlled standards and contains minerals, vitamins and a range of factors purported – but not evidenced – to improve health, such as long chain polyunsaturated fatty acids and complex oligosaccharides.

Preterm formula and NEC

The most recent Cochrane review includes 2,261 infants from 11 small trials in the analysis relating to NEC, which combined comparisons of formula and donor milk as sole diet and supplements.[17] They included two new trials: the MILK Trial, which was conducted in the United States, comparing pasteurised donor milk with preterm formula in extremely preterm infants receiving no or minimal own mother's milk[18] and our feasibility study PREMFOOD.[19] The MILK Trial failed to complete planned recruitment, but showed no significant differences in two year neurodevelopment (primary outcome), mortality or bloodstream infection. There was lower NEC (secondary outcome) in the pHDM arm. Of note, details of surgical NEC were not provided.[18]

In PREMFOOD, we compared fortified human milk feeds (own mother's milk supplemented if required with pasteurised donor milk), unfortified human milk feeds and feeds of own mother's milk supplemented if required with preterm formula. We found no significant between-group differences in growth or body composition at term or term plus six weeks. Two infants met rescue criteria for slow weight gain, one receiving exclusive feeds of pasteurised donor milk and one receiving exclusive feeds of own mother's milk. There were two deaths, both in infants exclusively fed own mother's milk. Two infants developed NEC; one with surgical NEC had only received own mother's milk and pasteurised donor milk; one with medical NEC had only received own mother's milk.[19]

The Cochrane authors conclude that the risk of NEC is halved through use of pasteurised donor milk in place of formula.[17] However, the diagnosis of NEC in the included studies was variable and included medical NEC, which is an imprecise diagnosis with many subjective features and hence is highly liable to ascertainment bias. No data are presented on surgical NEC. Of most importance is that neither sole nor supplementary comparisons show significant differences in important functional outcomes that would be important corroboration of benefit from pasteurised donor milk (mortality, invasive infection and neurodevelopment). Additionally, five of the 11 trials were conducted over 40 years ago when the patient population and clinical practice differed substantially from today, and eight of the 11 trials were judged to have high or uncertain risk of bias. Overall, this means the conclusion that use of pasteurised donor milk in place of formula reduces NEC is by no means definitive.

Pasteurised donor milk

Any pHDM used in the COLLABORATE study will be obtained from a UK milk bank under standard NHS processes. Human milk is a complex fluid, unique to each mother. In addition to nutrition, human milk contains several hundred biologically active molecules such as cytokines, enzymes, growth factors and immunoglobulins, as well as human milk oligosaccharides that regulate the development of the intestinal microbiome, mammary epithelial cell-derived extracellular vesicles, exosomes and microRNA.[20,21] Pasteurisation substantially reduces or destroys these biologically active non-nutritional components.[22] Donor milk also has lower nutrient content than preterm formula and own mother's milk. This is because nutrient content is lower in milk from mothers delivering at term and declines with duration of lactation. Donor milk is usually sourced from mothers delivering at full-term who have been lactating for several weeks.

Pasteurised donor milk and safety signals

There are emerging safety signals regarding adverse neurodevelopment in relation to use of pasteurised donor milk. The Canadian Domino Trial randomised very preterm infants to pHDM or preterm formula to make up any shortfall in own mother's milk. This study identified higher neuro-impairment at 18 months in the pHDM arm (27.2% v 16.2%; adjusted risk difference and a worse mortality/morbidity index (43% v 40%).[23]

In a causal inference analysis of five years' UK population-based data from the NNRD, we found almost 10% lower survival without NEC surgery to 34 weeks' gestational age (adjusted risk difference –9.8%) and a surgical NEC rate that was twice as high in very preterm infants receiving supplemental pHDM, compared with preterm formula.[24] The analysis for this study included sophisticated approaches to make the groups being compared as similar as possible. The unexpected findings may reflect unmeasured confounding (eg clinician tendency to use pHDM in infants they consider more at risk of NEC) but, nonetheless, also justification for a randomised controlled trial (RCT).

An observational study from the Canadian Neonatal Network of infants born less than 29 weeks' gestation evaluated the relationship between neurodevelopment and enteral feeding.[25] Infants that received any formula were excluded. These authors found that for each day a baby received pHDM instead of own mother's milk, there were statistically significant and highly clinically relevant greater odds of cognitive and language impairment at 18-24 months' corrected age. This study indicates that pHDM should not be considered equivalent to own mother's milk and may be harmful to neurodevelopment.

Routine protein-carbohydrate fortification

Fortifier used in the COLLABORATE study will be standard NHS stock cow milk-derived fortifier. When added to human milk, these fortifiers provide about 1.1g additional protein/100ml in an appropriate ratio with non-protein energy.

Fortification, growth and development

A current Cochrane review and meta-analysis compares fortified and unfortified human milk (18 trials; 1,456 infants) and finds no strong evidence of an effect on NEC (13 trials; 1,110 infants; relative risk 1.37 [95% confidence interval (CI) 0.72, 2.63]).[26] Only one RCT in this meta-analysis (245 infants), conducted in 1996, assessed neurodevelopment at 18 months and found no difference. Fortification can increase in-hospital growth but does not have any impact on body composition at term or term plus six weeks. Fortification also has no effect on long-term growth.

Routine fortification and potential harm

It is beneficial for a baby to receive as much own mother's milk as possible because of the non-nutritive components; feed volumes of 180-200ml/kg/day are widely used in the UK. However, preterm milk protein in the first month of lactation averages around 1.5g/100ml, but the range is wide (0.7-2.4g/100ml), hence routine fortification risks providing high protein intakes that may be damaging to neurodevelopment.[27] Concerns also exist because accelerated weight gain from fortification can increase the risks of adverse long-term consequences such as obesity, insulin resistance and hypertension.[27]

The findings of a systematic review and meta-analysis of planned high protein intake after birth for infants born preterm was that this might be harmful for survival, neurodevelopment and metabolism during infancy, and does not improve growth after the neonatal period. The authors concluded that protein intakes equal to or more than 3.5g/kg/d should not be recommended for children born preterm.[28]

How will safety be monitored in COLLABORATE?

Fortification is permitted in COLLABORATE infants who are randomised to the no-routine fortification arm if there is evidence of growth faltering due to protein inadequacy. Previous experience from our PREMFOOD feasibility study indicates this is likely to be a rare occurrence. In addition, high quality, rigorous RCTs have a data monitoring and steering committee that includes an independent chair and independent members. The remit of the data monitoring committee includes reviewing adverse reaction reports, as well as interim data analyses provided by an independent trial statistician, which includes all available outcomes. They will advise the trial steering committee of any evidence of harm arising as a consequence of participation, and whether one or both randomisations should stop on the basis of evidence of benefit or harm in any trial arm.

What did we find in focus group work?

Parent-patient-public involvement and engagement has played an integral part in the development of this proposal. Parents and former neonatal patients have a good understanding of the uncertainties we aim to resolve. Their contributions helped develop the COLLABORATE study in several ways.[29-31] A parent designed the COLLABORATE logo, while parents contributed to the development of COLLABORATE animations and co-designed the parent information leaflet to make it easy to understand and ensure it gives due emphasis to the benefits of own mother's milk.

Mothers relayed the stress they felt from pressure they experienced to express breast milk. Focus groups identified the importance of using language that does not add to guilt when mothers are unable to provide enough to meet daily requirements. Some parents expressed distaste at the thought of donor milk; others worried about formula. Several mothers said they felt offended at the suggestion by some healthcare professionals that being offered participation in COLLABORATE would reduce their motivation to express milk.

Parents also told us repeatedly about the anxieties caused to them if their baby's feed is changed when they are transferred to another neonatal unit and how clinicians varied in the information they provided. Parents expressed strong altruism in wanting to benefit other babies and described the relief they feel when they realise that COLLABORATE is trying to reduce uncertainties in care.

In focus group work, we also identified cognitive dissonance among some clinicians in which they recognised the uncertainties that justify the trial while simultaneously feeling anxiety because this clashed with their strongly held personal beliefs.[30]

Equity, diversity and inclusion

Parents are reliant on the information they are given and trust healthcare professionals to tell them honestly about the pros and cons of treatments. From a parent's perspective, exclusion from opportunity to decide whether they would like their baby to take part in clinical trials like COLLABORATE can exacerbate the sense of disempowerment many feel when their baby is in a neonatal unit.

Patients benefit from research participation by having the treatment allocated by randomisation, because this gives each baby a fair and equal chance of receiving the (unknown) optimal choice. Additionally, babies experience 'inclusion benefit', which is the phenomenon where patients participating in high quality RCTs have better outcomes than those who do not take part, regardless of the arm to which they are allocated.[32] Inclusion benefit likely arises because care is delivered along a clearly defined, closely monitored pathway.

There are variations in care processes, outcomes and experience of being partners in care, by ethnicity and neonatal network. Data from the NNRD show extremely preterm babies born to mothers of black ethnicity have the highest rate of receiving their own mother's milk at neonatal unit discharge and babies born to white mothers the lowest. In contrast, extremely preterm babies born to mothers of black ethnicity have the highest incidence of severe NEC compared to white and Asian infants (unpublished data). Data such as these emphasise the need to ensure that all infants are offered opportunity to participate in COLLABORATE and that the study population reflects the full extent of diversity in the UK.

We are committed to striving to give every family and every baby opportunity to take part in COLLABORATE, hence the study is open to all UK neonatal units either as recruiting or step-down sites. Parent information will be available in English, Welsh and the 10 other most prevalent UK languages (Polish, Romanian, Punjabi, Urdu, Portuguese, Spanish, Arabic, Bengali, Gujarati and Italian).

Conclusions

We invite all UK neonatal units to join the COLLABORATE study and help generate the evidence our vulnerable patients need to improve their outcomes. We urge you to respect the right of parents to be told about the uncertainties COLLABORATE aims to tackle and give them the opportunity to make their own informed choice. Together, we can finally resolve these uncertainties that have compromised the ability to deliver high quality care for too long.

Further information

Additional information about COLLABORATE, including PowerPoint presentations, parent videos, posters, fliers and details of investigators and partners can be found on the study website, which is updated regularly (www.imperial.ac.uk/neonatal-data-analysis-unit/collaborate). If you would like to join COLLABORATE or have any comments or questions, please contact us at collaborate@imperial.ac.uk.

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