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Research Article

Designing a precision-medicine platform trial to improve the nutritional care and intestinal health of very preterm babies: the COLLABORATE study

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Abstract

Background: Nutrition is essential for preterm brain development. Optimal nutrition is dependent upon gastrointestinal health.

Primary objective: To form a multiprofessional collaboration to design the world's first neonatal precision-medicine platform trial to test new and existing nutritional interventions for very preterm infants, to prevent and treat the serious gastrointestinal inflammatory disease necrotising enterocolitis and improve brain health and development.

Participants: Infants born very preterm (< 32 weeks gestation).

Data sources: Published literature; United Kingdom National Neonatal Research Database.

Methods: Engagement with parents, patients, clinical teams, and industry; literature reviews; simulation studies; mechanistic study design; collaborative study development.

Results: There was strong stakeholder support for the platform; seven interventions were selected from those proposed, four for immediate evaluation (pasteurised human donor milk; cow milk- and human milk-derived macronutrient fortifiers; probiotic), and three for subsequent incorporation (enteral arginine; enteral insulin;

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fluorescence image-guided surgery). We involved Australia/New Zealand neonatal units to shorten recruitment time, designed a precision-medicine platform trial, specified operational requirements and costs, developed engagement materials, and established parent–patient, independent scientific advisory and emerging investigator groups.
Limitations: National Institute for Health and Care Research processes required stage 1 application submission 8 months into the Accelerated Development Award. This was unsuccessful and did not include an opportunity to respond to feedback.
Conclusions: Stakeholders consider a neonatal precision-medicine platform trial a high priority, providing an efficient approach to establish the efficacy of treatments and the gestational age range of infants most likely to benefit, and to speed the pace of evidence generation to improve clinical care.
Future work: Reapplication, requiring a further stage 1 application.
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Background

Need

There is great and urgent need to accelerate the pace of evidence generation to improve newborn care and outcomes. There are around 650,000 births in the UK each year, of which about 6000 are very preterm (below 32 weeks' gestation). Over 95% of babies born very preterm survive, but of these, up to 60% have lifelong problems.[1] Mortality among very preterm babies has decreased substantially over recent decades but neurodevelopmental and cognitive outcomes – the principal determinants of adult educational, economic and societal attainment – have not improved.[2] There is also increasing recognition that, compared with their counterparts born at full term, these infants are at substantially higher risk of developing several chronic conditions typically associated with ageing; these include hypertension, ischaemic heart disease, renal impairment, type 2 diabetes, and the metabolic syndrome.[3] Women born preterm are more likely to deliver preterm themselves, an example of intergenerational passage of risk.[4]

There is also a huge need for research to improve the range of medicines and devices targeting newborn needs. Only one medicine (surfactant) has ever been developed especially for babies,[5] and over 90% of medicines used in newborn populations have inadequate information on dose, safety and efficacy.[6] Only 2.5% of trials in the Cochrane Central Register involve neonates;[7] two-thirds of Cochrane neonatal reviews are inconclusive because evidence is lacking or included trials are too small or methodologically poor.[8] An additional concern is that the number of clinical trials in paediatric populations is falling.[9]

Why a precision-medicine platform trial approach?

A platform trial offers opportunity for operational efficiencies, cost-effectiveness and rapid evidence generation through the ability to examine multiple interventions with a shared control, and enables cessation as soon as there is enough evidence of effectiveness or that continuing would be futile, as well as providing the ability to add additional intervention arms over time. The precision-medicine component would allow us to determine to whom these interventions should be targeted, as efficacy is likely to depend on the developmental maturity of the gut and the infant's sex. There are many uncertainties, and a neonatal platform would enable sequential testing of interventions – whether practice innovations, medicines, nutritional products or care processes – reducing uncertainties incrementally, testing new treatments, and avoiding lengthy start-up and close-down periods. The UK offers an excellent opportunity to establish a neonatal platform for several reasons. Care is delivered through well-integrated operational delivery networks; all NHS neonatal units contribute to a national data asset, the National Neonatal Research Database (NNRD), developed and managed at Imperial College London, that enables use of real-world data through a controlled data access mechanism, the Health Data Research UK (HDR UK) Innovation Gateway, thus reducing burden and cost; the UK has a national Research Ethics Service and nationally consistent processes for obtaining NHS approvals for research; and not least, the UK neonatal community has an excellent and well-established track record of collaborative research.

Necrotising enterocolitis

Necrotising enterocolitis (NEC) is an example of an area in which there is a worrying lack of evidence to guide clinical practice. NEC is an acquired inflammatory disease that predominantly affects the immature intestinal tract and involves bacterial invasion of the gastrointestinal barrier.[10] NEC presents insidiously or devastatingly acutely and is feared by healthcare practitioners and parents, especially as onset is usually after the initial period of physiological instability following very preterm birth. Management is

supportive, with surgery for perforated or necrotic bowel. Pathophysiology is poorly understood, and therapeutic targets are elusive. Enteral feeds, intestinal immaturity, ischaemic and other damage, and abnormal microbial colonisation are believed to play a role. Milk from a baby's own mother reduces but does not totally prevent NEC, and there are no other treatments known to work.[11] Optimal nutrition regimens that protect against NEC are uncertain. In addition, early nutritional interventions have long-term effects beyond possible effects on the risk of developing NEC. In addition to being an essential requirement for short-term survival, growth and development, early nutritional interventions have potential to improve the substantially increased risk among preterm populations for impaired cognitive development and ultimately long-term risk of poor cardiometabolic health. However, which nutritional interventions are suitable for which infants, and their mechanisms of action, are unknown. Understanding the relationships between nutrition, gut health, and brain development and function are thus critical to improving lifelong well-being for children born very preterm.

Importance

Necrotising enterocolitis affects 5–10% of very preterm infants,[10] and incidence is inverse to gestational age.[11] In high-income settings, NEC is a leading cause of death, impairment and healthcare costs.[10] Around 5% of very preterm babies need surgery for NEC, and up to twice as many have less severe disease that disrupts feeding, prolongs hospital stay, increases healthcare costs, and necessitates prolonged parenteral nutrition with attendant risks of systemic sepsis and liver dysfunction. Up to 40% of NEC surgical cases die, and up to 60% of survivors are left with lifelong sequelae that include gastrointestinal and neurodevelopmental problems.[12] According to national and international definitions, NEC is a rare disease, in that it affects < 1 in 2000 people within the general population.[13] In the UK, there are about 260 NEC deaths and/or surgeries each year.[11] Multicentre collaboration is therefore essential to recruit enough patients into trials.

Research to prevent and treat NEC is important now because fear that nutrition affects risk results in highly variable practice which compromises patient safety and leads to anxiety for parents and confusion among staff. Therapeutic creep, promotion of commercial nutrition products, and proliferation of non-evidenced consensus guidelines also illustrate the importance of resolving uncertainties rapidly. Stakeholders consistently rank research – including nutritional strategies to prevent and treat NEC – a priority, as indicated consistently over the last decade in prioritisation studies including by the James Lind Priority Setting Partnership and British Association of Perinatal Medicine.[14–16]

Aims and objectives

Aims

Our goal over many years has been continuous improvement in the evidence base to support personalised care pathways for sick and preterm infants through efficient, cost-effective collaborative clinical research. The primary aim of the Accelerated Development Award was to build on our prior work, conducted over several years, and accelerate completion of a detailed master protocol, agreed by parent–patient groups, clinicians and academic/industry partners, for a precision-medicine platform trial in the UK and international settings, to be submitted as a stage 1 application in May 2023, with anticipated stage 2 application in September 2023, planned start date of April 2024, and end date in 2029. The platform trial would test the efficacy of a pipeline of nutritional interventions in very preterm neonates, and hypotheses regarding effector mechanisms. It would advance generalisable learning around platform study design, UK and international regulation, and best practice in relation to parent–patient–clinician–industry involvement.

Objectives

Specific objectives for the accelerated development phase were to finalise (1) the research team and (2) the selection of initial interventions; (3) design the platform trial; complete (4) mechanistic study protocols, (5) a stakeholder involvement, engagement and communications plan, and (6) research ethics application(s) for UK and non-UK sites; and (7) secure operational readiness.

Methods

Research team and selection of interventions

We conducted multiple webinars, online discussions and focus groups with clinical teams, parents and patients in the UK, Australia and New Zealand, to explain the platform trial and to invite both proposals for interventions to test and expressions of interest in joining the investigator group. Australia and New Zealand have neonatal populations and clinical practice that is very similar to those in the UK; their inclusion would reduce time to recruit the required number of patients, hence resolve uncertainties more rapidly, and achieve patient benefit more quickly.

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We engaged with the manufacturers of all probiotics marketed in the UK as a prophylactic against NEC, to gauge their interest in evaluating the efficacy of their product. These are marketed as nutritional supplements, and none has evidence of efficacy in the very preterm population. We also contacted companies developing pharmaceutical agents to prevent or treat NEC.

Patient and public involvement

We consulted with stakeholder groups to discuss the interventions and obtain their views on the final selection, the rationale for our approach, and our study design. We also sought stakeholder views on specific issues such as the content of parent information leaflets, and our communications strategy. We drew upon our well-established parent/former patient groups. These are a 12-member parent advisory group, 12-member former patient advisory group, 30-member ancillary advisory group, and approximately 500-member consultation group. We also worked closely with the Adult Preemie Advocacy Network (APAN) established by young people who were born preterm; Bliss, the national UK charity for babies born preterm or sick; the European Foundation for the Care of Newborn Infants; and Miracle Babies Foundation, an Australian organisation supporting premature and sick newborn babies and their families.

Equality, diversity and inclusion

We purposively sought participation in focus groups to try to achieve involvement that was representative of the diversity of preterm infant families. We are also very aware that securing the involvement of fathers and former patients with disabilities requires specific attention. Underserved groups are disproportionately represented in neonatal care; hence our strategy incorporates the INCLUDE framework.[17]

Data sources

We searched the Cochrane Library for relevant systematic reviews and meta-analyses. We searched PubMed for recent publications that had not been included in the Cochrane outputs; ClinicalTrials.gov and ISRCTN for ongoing or planned trials; and neonatal conference abstracts for unpublished studies. We drew upon a national data asset, the NNRD, to obtain baseline data and to conduct exploratory analyses of outcomes in relation to proposed interventions.

Platform study design

We used 5 years of population data for England and Wales (36,078 very preterm babies) from the NNRD to conduct detailed simulation studies. We employed FACTS version 7 [FACTS (Fixed and Adaptive Clinical Trial Simulator), URL: www.berryconsultants.com/software/facts/] to examine a range of outcomes and design parameters for each domain, and to estimate sample sizes, statistical triggers and placement of adaptive analysis. A Bayesian approach was used to determine stopping rules at each adaptive analysis based on estimating posterior probability of success. A range of potential trial result scenarios were explored for designing a precision-medicine platform trial on treating preterm babies with a multiple feeding option. These included varying the sample size, primary outcome rate in the control and treatment groups, recruitment rate, time to last follow-up, withdrawal and loss to follow-up rates, randomisation allocation ratio and type I and type II error trade-offs.

Operational readiness

Following application, the Imperial Clinical Trials Unit accepted COLLABORATE onto their portfolio. We collaborated with their staff to develop trial processes and determine costs.

Results

Primary output

The primary output of the Accelerated Development Award was the Stage 1 EME application.

Description of the platform trial, primary outcomes, participating neonatal units, eligibility, research efficiencies and real-world data source

Platform trial

We developed COLLABORATE: an international, precision-medicine, randomised, controlled, adaptive, real-world data-facilitated platform trial to evaluate the efficacy and mechanisms of action of interventions to prevent or treat neonatal NEC and provide ongoing infrastructure for future studies to improve newborn care. COLLABORATE is a real-world data-facilitated, Bayesian adaptive multifactorial enrichment trial comprising five domains and seven interventions. We designed the platform so that additional domains and interventions can be added at subsequent time points. We planned to initiate domains 1–3, examining the prevention of NEC, immediately (first recruitment at 9 months), and domains 4–5, examining surgical treatment of NEC and postoperative bowel rehabilitation, at the end of year 2. The platform has national reach, international contributors, and a simple enrolment process embedded in clinical practice. *Figure 4* includes a platform flow diagram.

Primary outcomes
For domains 1–3, survival without NEC surgery to 34 weeks postmenstrual age (PMA); for domains 4 and 5, duration of parenteral nutrition.

Participating sites
All UK neonatal units are eligible to participate as recruiting or transfer sites (n = 181), restricting participation for domains 4–5 to neonatal surgical centres. Interest is high, already exceeding 50%, which would be sufficient to recruit to target. We planned to involve around 15 Australia/New Zealand neonatal units to increase recruitment in domain 3 (three arms) and domains 4–5 (surgical cases).

Participant eligibility
Birth at < 32 weeks' gestation and no condition precluding enteral feeding. Babies can participate in multiple domains. Informed parent consent obtained.

Research efficiencies
We planned to reduce burden and cost in several ways. We would acquire most UK platform trial data from the NNRD, a Health Research Authority-approved National Information Asset currently supporting around £25M research (see *Real-world data source*). Trial data for Australia/New Zealand would be submitted using electronic Clinical Record Form using a previously developed, dedicated online portal. We would also use a digital version of a previously developed and tested, validated, National Institute for Health and Care Excellence-recommended parent questionnaire to assess age 2-year cognitive and language development.[18] We employed statistical efficiencies to minimise the sample size required for each domain.

Real-world data source
The NNRD contains a detailed, standard, quality-assured data extract (Neonatal Data Set; NHS Information Standard DAPB1595) from the electronic patient records of all admissions to all 181 NHS neonatal units in England, Wales and Scotland.[19] The quality of NNRD data is high, as shown by objective evaluation and use for high-impact outputs including policy development, legislative change and medicines studies. The level of missing data in the NNRD has fallen steadily over time, is now very low, and can be viewed publicly on our website (www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data-analysis-unit/nnrd-data-visualisations/). Missingness for nutritional data is now < 10%, and rates for age 2-year neurodevelopmental outcomes are comparable to research studies.[20] However, the issue of missing data is wholly addressed by the approach we employ when using the NNRD for prospective studies. In prospective studies, we monitor NNRD data throughout the study and contact neonatal units to ask them to enter any that are missing into the infant's electronic patient record, which we receive into the NNRD at the next data extraction. This means not only that missing data are highly unlikely but also that there is no lengthy post-recruitment period chasing these items.

Research questions
These are expressed below in PICO [population (P), intervention (I), comparator (C), outcome (O)] format.

Domain 1: In babies < 29 weeks' gestation for whom there is insufficient own mother's milk (OMM) (P), does pasteurised human donor milk (pHDM) (I), compared with preterm formula (C) as a supplement, improve survival rate to 34 weeks PMA without NEC surgery (O)?

Domain 2: In babies < 29 weeks' gestation (P), does a daily multistrain probiotic [Labinic® (Biofloratec, Walton-on-Thames, UK, other products to be evaluated later)] (I) compared with placebo (C), improve survival rate to 34 weeks PMA without NEC surgery (O)?

Domain 3: In babies < 29 weeks' gestation (P), does routine macronutrient fortification with cow milk fortifier (I) or human milk fortifier (I), compared with no routine fortification (C), improve survival rate to 34 weeks PMA without NEC surgery (O)?

Domain 4: In babies < 32 weeks' gestation who require NEC surgery (P), does fluorescence-guided resection (I) compared with visually guided resection (C), reduce the duration of postoperative parenteral nutrition (O)?

Domain 5: In babies < 32 weeks' gestation in whom postoperative care is initiated after NEC surgery (P), does enteral recombinant human insulin (I) or enteral arginine (I), compared with placebo (C), reduce the duration of postoperative parenteral nutrition (O)?

Evidence review
Here we summarise evidence justifying the need to evaluate the efficacy of the selected interventions.

Pasteurised human donor milk
A baby's OMM is associated with reduced NEC,[11] but on average mothers delivering very preterm express only about half the required volume.[21] pHDM and preterm formula are the only enteral options to supplement a shortfall in OMM.

Pasteurised human donor milk is not equivalent to OMM, as pasteurisation reduces or destroys many non-nutritive components such as immunologically active

agents, growth factors and probiotic species. The current Cochrane Review and meta-analyses [12 randomised controlled trials (RCTs); *N* = 1879] comparing pHDM and formula find reduced NEC only in sole diet comparisons and no benefit in other important outcomes as either sole or supplementary feeds [NEC risk ratio (RR) 1.56 (95% CI 0.98 to 2.47); all-cause mortality 1.02 (95% CI 0.73 to 1.44); 18-month neurodevelopmental disability 0.92 (95% CI 0.4 to 2.1)]. The Cochrane Review concludes that the evidence is inadequate to recommend pHDM over formula when a supplement is needed for OMM.[22]

Of concern is the possibility of harm from use of pHDM. The low nutrient density of pHDM may be inadequate to support the growth and brain development of very preterm babies. RCTs show that growth is slower with pHDM, even when it is nutrient-enriched.[22] A Canadian trial (DOMINO) comparing nutrient-enriched pHDM or preterm formula as OMM supplement showed more children randomised to pHDM with neuro-impairment at 18 months [27.2% vs. 16.2%; adjusted risk difference (RD) 10.6% (95% CI 1.5% to 19.6%)] and worse mortality/morbidity (43% vs. 40%).[23] Our analysis of UK population data found almost 10% lower survival without NEC surgery in very preterm infants receiving OMM supplemented with pHDM compared with formula [adjusted RD −9.8% (95% CI −11.4% to −8.2%)]; the poorer outcome with pHDM increased with decreasing gestational age, with the largest difference at 24 weeks [−51.5% (95% CI −58.8% to −44.3%)], reducing to minimal at 31 weeks.[24] The Milk Trial (*n* = 483) conducted in the USA, compared pHDM with preterm formula in extremely preterm infants receiving no or minimal OMM.[25] This failed to complete planned recruitment but showed no significant differences in 2-year neurodevelopment (primary outcome), mortality or bloodstream infection. There was lower medical NEC (secondary outcome) in the pHDM arm. Details of surgical NEC were not provided. These data reinforce the possibility that interventions may have different impacts in relation to gestational age.

Currently only about 20% of very preterm babies receive any pHDM. If pHDM is the optimal supplement, all very preterm babies should have equitable access. The 2023 British Association of Perinatal Medicine's 'Framework for Use of Donor Milk' highlights the urgent need for research to identify the optimum supplement for OMM.[15]

Probiotics

The use of probiotic preparations is growing rapidly around the world, although evidence of their efficacy in protecting very preterm babies against NEC is weak. Mechanisms are unknown, but the premise is that probiotics protect against the aberrant gut microbial colonisation and reduced diversity characteristic of NEC. Probiotics are not a UK standard of care, and international statements make only conditional recommendations, but a growing number of products are available as nutritional supplements (a single product is licensed as a medicine in the EU/USA, and none in the UK). Meta-analyses indicate that probiotic supplements may reduce NEC [54 trials; *N* = 10,604; RR 0.54 (95% CI 0.45 to 0.65)], but evidence certainty is judged low because of a very high risk of bias, and no benefits have been shown in very preterm babies (8 trials; *N* = 1712).[26,27] We planned to evaluate probiotics marketed in the UK, initially a three-strain (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium infantis*) product already used in several centres.[28]

Protein–carbohydrate fortification

Fortified human milk is not a UK standard of care and received by only 45% of UK very preterm infants.[29] The concern is that fortification with highly processed cow milk products will increase NEC, but without fortification macronutrient intake, principally protein, will be inadequate. A counterconcern is that routine fortification risks exposing babies to high protein intakes dangerous to neurodevelopment, renal and metabolic health. The current Cochrane Review of fortified versus unfortified human milk (eight trials; *N* = 1456) finds no evidence for an effect on NEC [RR 1.37 (95% CI 0.72 to 2.63)].[30] Only a single trial (*N* = 245) in 1996 assessed neurodevelopment (no difference); none evaluated renal or metabolic outcomes.[30]

Commercial fortifiers prepared from pooled human milk from paid donors are now becoming available, including from a UK company, Neokare, that manufactures a range of human milk products (also see *Potential sample sizes*). However, the current Cochrane Review concludes that efficacy has not been shown for these new commercial pooled human milk products.[31] A recent trial not included in this review, conducted in Sweden and comparing human and cow milk fortifiers, also showed no benefit from the former.[32]

We previously conducted a pilot study, Premfood (NCT01686477) that showed our planned comparison is safe, acceptable and feasible.[33] Premfood was an open, parallel feasibility trial in which we randomised infants born between 25^{+0} and 31^{+6} weeks' gestation within 48 hours of birth to receive unfortified human milk (unfortified mother's milk ± unfortified pHDM supplement), fortified human milk (fortified mother's milk ± fortified pHDM supplement), or unfortified mother's milk ± preterm formula supplement from birth to 35^{+0} weeks PMA. Randomisation was acceptable to parents and clinical teams. There were no safety concerns and no significant between-group

differences in the primary outcome, total adipose tissue volume at term [unfortified human milk: mean 0.870 l, standard deviation (SD) 0.35 l; fortified human milk: mean 0.889 l, SD 0.31 l; preterm formula: mean 0.809 l, SD 0.25 l; $p = 0.66$] or term plus 6 weeks, or in regional adipose tissue volumes and anthropometry at either time point.

Indocyanine green fluorescence-guided surgery

Indocyanine green fluorescence-guided surgery is a promising technique to evaluate bowel perfusion during NEC surgery. Proof of concept has been shown in very preterm babies, reducing the length of bowel resected, need for stoma creation, surgical complications and non-operability diagnosis.[34] It is in limited use in neonatal surgical centres in Australia (G Thomas, Head of Surgery, Children's Hospital Westmead, New South Wales; personal communication, 2023), but not thus far in the UK. No studies have assessed the efficacy of indocyanine green fluorescence-guided surgery against traditional visually guided NEC surgery.

Enteral arginine and insulin

Arginine, a conditionally essential amino acid, has preliminary evidence of efficacy in reducing NEC-related death [three RCTs; $N = 285$; RR 0.18 (95% CI 0.03 to 1.00)][35] in very preterm babies, and is widely used in postoperative bowel rehabilitation in other age groups.[36] An international, multicentre, double-blind, placebo-controlled randomised trial of recombinant enteral insulin in very preterm babies ($N = 303$) found no safety concerns, improved feed tolerance and reduced NEC (6% low dose; 5% high dose; 10% placebo).[37]

Other relevant unpublished and published studies

Lactobacillus reuteri probiotics are being evaluated in NCT05710575 (sponsored by Biogaia; conducted in Pakistan; $N = 100$) and NCT03978000 (sponsored by IBT; international trial; $N = 2158$; end date December 23; this product has US Food and Drug Administration/European Medicines Agency orphan drug designation for NEC prevention). NCT03797157 (sponsored by Prolacta; conducted in Sweden; $N = 228$) compared supplementation of OMM with human and cow milk fortifiers and found no difference in NEC or other outcomes.[32]

Simulation studies

Potential sample sizes

We initially considered total sample sizes (including withdrawal/loss to follow-up) of 3000, 3500 and 4000 babies for domains 1–3, and 200, 300 and 400 babies for domains 4 and 5. Our interest was in the between-arm RDs for domains 1–3 and hazard ratios (HRs) for domains 4 and 5. We calculated the power of these sample sizes to detect minimum clinically important differences (MCIDs) and the relevant type I error using a Bayesian approach. Adaptive analyses were explored with placements after 50% of participants had been recruited and then every 12, 18 and 24 weeks.

Decision rules for futility and efficacy

The definition for efficacy (benefit) was defined as a high probability ($\pi_1 S$) for the RD/HR being in favour of the intervention, exploring differing predetermined margins of superiority (γ_1 and θ_1). The definition for futility was defined as a low probability ($\pi_2 S$) of a RD/HR in favour of the intervention. Otherwise, the trial would be deemed inconclusive and would continue recruiting until reaching the maximum sample size. Initial stopping rules for efficacy and futility are defined below.

Efficacy

If $P(\text{RD} > \gamma_1) > \pi_1 S$ for domain 1–3 and $P(HR > \theta_1) > \pi_1 S$ for domain 4–5 trial stopped for efficacy where RD = *RE-RC* and HR is hazard ratio (RD = *HE*/*HC*); here *RE* and *RC* denote risk of primary outcome in experimental group and active control, respectively. Here γ_1 is a positive value corresponding to benefit for the active arm. Note that if the RD is positive, then the result favours the experimental treatment.

Futility

And if $P(\text{RD} > \gamma_2) > \pi_2 S$ for domains 1–3 and $P(HR > \theta_2) > \pi_2 S$ for domains 4–5 trial stopped for futility; γ_2 here is considered as a positive value of benefit for the active arm that is unimportant.

Design parameters for potential trial outcome scenarios are shown in Table 1. Simulation study results were viewed graphically to identify optional triggers to maximise the posterior probability across domains and strata (see *Appendix 1*).

Stopping rules for domains 1–3

An arm will stop for futility when $P(\text{RD} > 0\%) < 0.10$.

An arm will stop for superiority when $P(\text{RD} > 0.5\%) > 0.90$.

Expected sample size = 2736.

Maximum sample size = 4000.

Stopping rules domains 4–5

An arm will stop for futility when $P(HR > 1.19) < 0.05$.

An arm will stop for superiority when $P(HR > 1.19) > 0.90$.

TABLE 1 Design parameters for potential trial outcome scenarios

Design parameters for simulation scenarios	Domains 1–3	Domains 4–5
Maximum target sample size examined	3000, 3500, 4000	200, 300, 400
Recruitment rates examined	19 babies per week	10 babies per month
Dropout rate assumed	10%	10%
Allocation ratio used	1 : 1	1 : 1
Frequency of adaptive analysis explored	First at 50% max target SS and then 12 weeks, 18 weeks and 24 weeks	First at 50% max target SS and then 12 weeks and 18 weeks
MCID assumed	3% and 5% over control	30% over control
Using triggers for efficacy: $P(RD > \gamma_1) > \pi_1 S$ $P(HR > \theta_1) > \pi_1 S$	Explored all combinations of: γ_1 = 0%, 1%, 1.5%, and $\pi_1 S \geq 0.8$–0.99	Explored all combinations of: θ_1 = 5, 10 median time, and $\pi_1 S \geq 0.7$–0.85
Using triggers for futility: $P(RD > \gamma_2) > \pi_2 S$ $P(HR > \theta_2) > \pi_2 S$	Explored all combinations of: γ_2 = 0%, 1%, 1.5%, and $\pi_2 S < 0.025$ and 0.050	Explored all combinations of: θ_2 = 5, 10 median time, and $\pi_2 S < 0.050$, 0.100

SS, sample size; $\pi_1 S$ and $\pi_2 S$, probability of intervention superior to control.

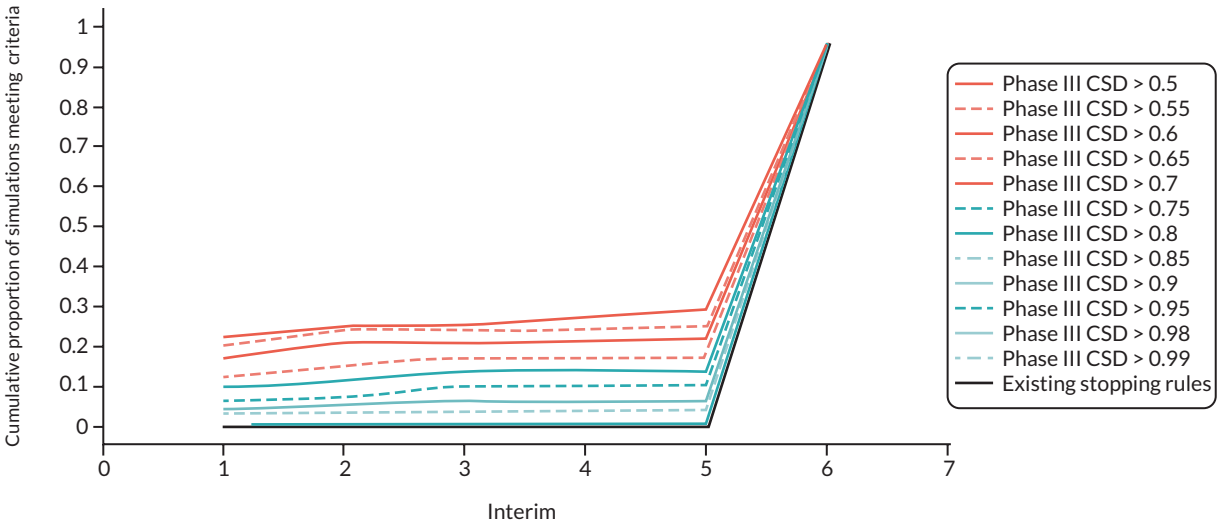

FIGURE 1 Cumulative proportion of simulations satisfying superiority criteria by each interim under a null scenario for a maximum of six analyses.

Expected sample size = 363.

Maximum sample size = 400.

Figures 1 and *2* are examples of the graphs showing the proportion of simulated trials incorrectly stopping early under both the null and beneficial scenarios (3% and 5% superiority). The results are plotted for a maximum of six interims. *Figure 1* shows the proportion stopping for success (type I error) in the null (futile) scenario for different thresholds (stopping rules e.g. $\pi_1 S > 0.5$–0.99) up to the fifth interim and then all arms at the sixth analysis as the maximum sample size is reached. We can see that using $\pi_1 S$ at 90% [clinically significant difference (CSD) > 0.9] provides the lowest type I error rate. Similarly, *Figure 2* displays the proportion stopping for futility under the beneficial scenarios (3% absolute improvement in primary outcome) up to the fifth interim and then all arms stop at the sixth analysis. From this graph it can be seen that a threshold of 10% (CSD < 0.1) offers the second lowest proportion of incorrect early stopping (type II error) overall, and this is selected as small enough trading off against other sample size parameters (data not shown).

Figure 1 displays the results for incorrectly stopping early for benefit under the null assumption (no treatment effect across the precision-medicine factor strata). CSD < X.XX is the probability of exceeding the CSD threshold used to trigger a benefit. The vertical axis displays the proportion of trials in simulations that were stopped.

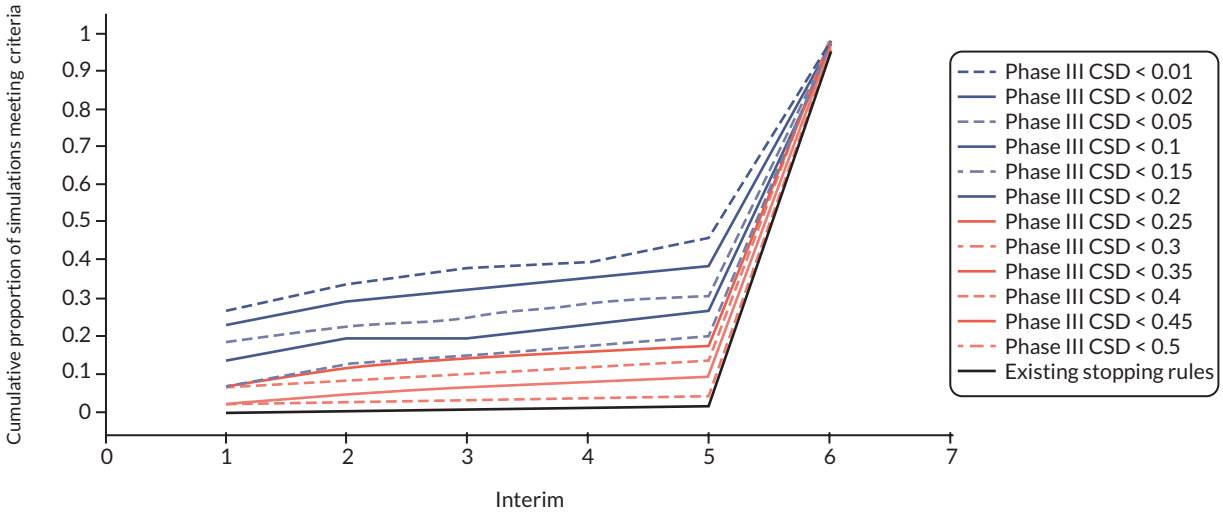

FIGURE 2 Cumulative proportion of simulations satisfying futility criteria by each interim under a 3% superiority assumption for a maximum of six analyses.

Figure 2 displays the results for incorrect stopping early for futility when there is a 3% intervention benefit. CSD < X.XX is the probability of exceeding the CSD threshold used to trigger a benefit. The vertical axis displays the proportion of trials in simulations that were stopped.

Simulation study graphical results are shown in *Appendix 1*.

Statistical analysis plan

For within-strata comparisons for domains 1–3, the principal approach was a Bayesian logistic regression model with a vague prior; that is, no prior information regarding the intervention effects would be included in the model. The model would be stratified by precision-medicine factors and adjusted for site and country. The posterior distribution of the intervention odds ratio (relative to control arm) would be estimated using Markov chain Monte Carlo techniques, and the mean of this distribution with 95% credibility interval would be reported alongside the posterior probability of exceeding the relevant stopping rule thresholds. The stopping rules above would be used to guide decisions by the independent data monitoring and ethics committee on when to stop intervention arms. The trial would stop after the maximum sample of 4000 recruits (pro rata per arm) if no triggers were met and after a maximum of six analyses. The first interim would occur after at least 50% of participants were recruited, to reduce the type I error. For domains 4–5, the same approach to the analysis would be used but with a Cox proportional hazards model. The models would contain an interaction term to estimate the intervention effects in each stratum.

Parent and patient involvement and engagement

Parent/patient representatives are coinvestigators on the stage 1 application and coauthors on this report. Our intention was that they would also be members of the Trial Management Group and the Trial Steering and Data Monitoring and Ethics Committees. Their contributions are summarised below.

1. Our focus group work elicited novel insights. We found that parents report that opportunity to resolve uncertainties by trial participation can help reduce their anxieties about having a baby in neonatal care.[38]
2. We also identified cognitive dissonance among some clinicians, wherein though recognising the lack of evidence to guide nutritional regimens for very preterm babies, their personal biases prevented them from putting the uncertainty to the test of randomisation.[39]
3. Our pilot trial, Premfood (see *Protein–carbohydrate fortification*) showed that parents found randomisation to the specified interventions acceptable.
4. Parents advised on the format of the trial information leaflet and cocreated the proposed version.
5. A parent designed the COLLABORATE logo (*Figure 3*).
6. With Bliss and APAN, we coproduced a video animation directed at parents, families, and clinical teams to achieve wide understanding, knowledge, and awareness of the platform trial, and to promote participation by clinical teams and parents.

Research ethics approval

As the proposed platform study was rejected at stage 1 application, 8 months into the Accelerated Development Award, we did not submit a protocol for research ethics approval.

This article should be referenced as follows:
Modi N, Chehrazi M, Boardman J, Boyd A, Bradley P, Cirelli C, *et al*. Designing a precision-medicine platform trial to improve the nutritional care and intestinal health of very preterm babies: the COLLABORATE study [published online ahead of print February 26 2025]. *Efficacy Mech Eval* 2025. https://doi.org/10.3310/LMHT3521

Trial registration details

As above (see *Research ethics approval*), this was not applicable.

Trial data flows

The majority of trial data would flow from the NNRD into the platform database, thus minimising data collection burdens traditionally imposed upon clinical staff. Minimal ancillary data (e.g. documenting consent, randomisation, safety data and withdrawal) would be entered directly onto a dedicated web-based portal managed by the Imperial Clinical Trials Unit. The portal would also be used for all data submission by participating neonatal units in Australia and New Zealand. Trial staff would check data regularly for completeness and promptly contact contributing sites about missing data. This would ensure availability for interim analyses, and no end-of-study time allocation to chase missing data. *Figure 4* depicts trial data flows.

FIGURE 3 COLLABORATE logo.

Mechanistic studies

The effect of nutritional interventions on encephalopathy of prematurity

Background and rationale

Preterm birth is a leading cause of cerebral palsy, cognitive impairment, autism spectrum disorder and psychiatric disease later in life.[40] Between 30% and 50% of infants born below 32 weeks' gestation grow up with a disability.[41] The neural basis of functional impairment includes dysmaturational processes in white matter that lead to hypomyelination, dysconnectivity of developing neural networks, and altered development of cortical and deep grey matter, collectively termed encephalopathy of prematurity (EoP).[40,41] Advanced magnetic resonance imaging (MRI) captures EoP in preterm infants at term equivalent age and is an objective intermediate phenotype for studying upstream determinants of brain health[41] and evaluating brain effects in interventional studies.[41–44]

Observational and randomised controlled studies provide strong evidence that nutritional exposures during neonatal intensive care can impact brain development and long-term neurodevelopmental and cognitive outcomes.[45] High compared with low exposure to human milk during neonatal intensive care is associated with enhanced white matter connectivity and a cortical image phenotype that more closely resembles the brain morphology of term-born infants, suggesting that nutritional factors attenuate EoP.[45,46] The relationship between nutrition and brain development may be mediated by micro-/macronutrients and non-nutritive factors in milk, such as immunoglobulin, lactoferrin, lysozyme, human milk oligosaccharides and microRNA (miRNA), and by effects on the gut–brain axis mediated by the gut microbiome and its metabolites. These exposures are modified by the feeding interventions

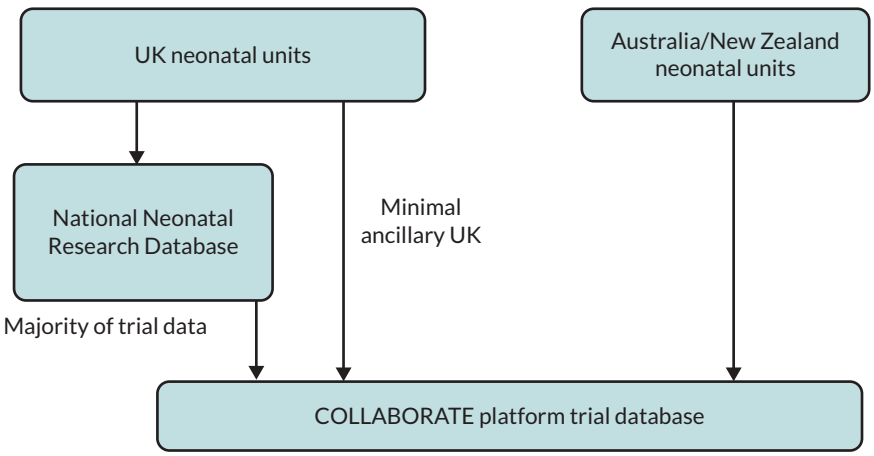

FIGURE 4 Platform trial data flows.

and probiotics which COLLABORATE is designed to test. Therefore, COLLABORATE provides a unique opportunity to investigate the neural mechanisms that link nutrition with neurodevelopment in preterm infants.

Aim

Our translational aim is to identify the safest and most effective nutritional regimen to reduce the incidence of EoP and promote healthy brain development after preterm birth. This nested substudy will improve causal inference about associations between exposure and outcome by determining whether the nutritional interventions directly modify EoP, or whether the associations are explained by confounding factors. We planned to test the hypotheses that one or more of the following interventions decrease the prevalence of EoP after preterm birth:

- pHDM versus formula enteral milk supplement when there is a shortfall in OMM
- probiotic supplementation versus placebo
- routine versus no routine macronutrient fortification of breast milk.

Methods

A nested substudy is the most appropriate and efficient approach. Based on computational modelling[47] and prior precedent from neonatal neuroprotection trials, a study of 60 infants in each treatment group is estimated to detect a 10% difference in fractional anisotropy with 80% power and two-sided 5% significance. Hence, we proposed to study 120 infants born below 32 weeks' gestation at the Royal Infirmary of Edinburgh, a regional centre that provides neonatal intensive care for 100–120 infants born at < 32 weeks' gestation per annum. They would undergo 3T brain MRI using a research-dedicated Siemens MAGNETOM® Prisma clinical scanner (Siemens Healthcare, Erlangen, Germany) and 16-channel phased-array paediatric head and neck coil. The MRI protocol is conditional upon in-house expertise and is not transferrable to other centres.

For each of the three interventions, we planned to carry out a groupwise comparison of white matter microstructure (fractional anisotropy values using tract-based spatial statistics) and cortical morphology and microstructure using published methods.[47,48] Analyses would be adjusted for gestational age at birth, age at image acquisition, and covariates from the following list that are imbalanced after randomisation: maternal age, maternal obesity, Scottish Index of Multiple Deprivation, mode of delivery, pre-eclampsia, sex, birth weight *z*-score, sepsis, intraventricular haemorrhage and bronchopulmonary dysplasia.

Gut health

Background

Maintaining a resilient barrier function of the developing gut is essential to preventing NEC. The gut epithelium is a highly organised barrier that orchestrates digestion and absorption of nutrients for growth, facilitates immune sampling and tolerance to intestinal bacteria, and is compartmentalised, maintaining a gradient of luminal bacterial cell density from proximal to distal colon that optimises sensing and delivery of nutrients to the host. In the preterm gut, epithelial immaturity impairs function, an impairment which is further exacerbated by development being compromised by fetal growth restriction and an aberrant microbiome. However, the mechanisms through which these result in NEC are largely unknown.

Hypotheses

We propose to test the hypothesis that the domains 1, 2 and 3 (pHDM; multistrain probiotic supplement; routine macronutrient fortification) and domain 5 (enteral insulin; enteral arginine) interventions affect gut barrier functions.

Methods

Using commercially available enzyme-linked immunosorbent assays, we will assess gut barrier integrity and permeability using the established markers lipopolysaccharide binding protein (LPSBP) and soluble CD14 (sCD14). LPSBP is increased in response to endotoxin translocation across the epithelial barrier and has been shown to reflect gut barrier function in young children with enteropathy,[49] while sCD14 is released by macrophages upon stimulation with bacterial lipopolysaccharide; thus, both markers give an assessment of gut hyperpermeability. We will also measure myeloperoxidase, neopterin and calprotectin as established markers of gut inflammation, and zonulin-1 as a marker of epithelial tight junction integrity.

Planned separately funded mechanistic substudies

Human milk microRNAs

Human breast milk is known to contain over 1000 different miRNAs. These small non-coding RNA molecules which regulate mRNA translation have the potential to enter the neonatal circulation and influence infant metabolism. They therefore represent a novel mechanism by which the composition of human milk can influence development of the infant. We propose to measure human milk miRNAs in samples from domains 1–3 and establish whether differences in the milk miRNA profile correlate with those in the infant circulation and whether they are associated

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with infant outcomes such as EoP, as indicated by advanced MRI. This substudy will provide novel information about nutritional mediators of brain development and specific mother–infant interactions. We will maximise research efficiency by obtaining samples of OMM, pHDM and infant serum from COLLABORATE recruits at the Royal Infirmary of Edinburgh. We have already secured funding for an early-career researcher from the Universidae Federal de Sao Paulo, Brazil, who will spend an internship in the UK in 2024, to establish protocols and generate pilot data for the full study for which we will seek additional funding.

Probiotic supplementation and multidrug-resistant organisms

Domain 2 offers an important opportunity to test the hypothesis that probiotic supplementation in very preterm neonates reduces neonatal unit-wide prevalence of multidrug-resistant organisms. This would be a powerful indirect strategy to reduce neonatal mortality and morbidity. We will obtain and store stool samples to examine multidrug-resistant organism carriage in a separately funded study.

Genetic variants as future precision-medicine factors

Genetic variants leading to the upregulation of signalling by Toll-like receptor 4, an innate immune receptor, may increase NEC risk. Other putative signalling regulators are nuclear factor κB1, the small glycolipid transport protein ganglioside GM2 activator, coreceptor molecule lymphocyte antigen 96, and single Ig interleukin-1 related receptor. Variations in NEC by sex and race are considered due to genetic variations within these groups. We have therefore discussed the possibility with Genomics England of accessing data from the landmark neonatal whole-genome sequencing programme. They have confirmed that the programme will be rolled out progressively across the UK during COLLABORATE and that data will be available to external research groups. We therefore propose a separately funded, post hoc reanalysis of COLLABORATE and Genomics England data to identify genetic variants that might be relevant precision-medicine factors for future targeted drug studies to prevent or treat NEC.

Discussion

The 1-year Accelerated Development Award enabled us to assemble a diverse, multiprofessional group of coinvestigators with expertise in clinical neonatology, trial design, mechanistic studies, industry engagement, use of real-world data, parent and patient involvement and engagement, and parents and patients. We identified strong UK and international support for establishing a platform trial that would in the first instance evaluate pressing comparative effectiveness uncertainties, and a range of probiotics aimed at reducing NEC, as well as an intraoperative imaging technique and postoperative bowel rehabilitation medications. We showed that our planned approach was acceptable to clinical teams, parents and patients, and likely to be feasible given the number of participating neonatal units and their patient throughputs.

Our approach has several strengths. It builds on extensive prior work, and both comprehensive literature review and stakeholder feedback confirm there is powerful justification to examine the selected interventions. The likelihood of patient benefit is extremely high, and the platform is likely to be highly cost-effective by primarily using existing real-world data from a well-established UK national data asset that has a track record of supporting high-quality research. However, our stage 1 application, submitted 8 months into the 12-month Accelerated Development Award, was unsuccessful.

Conclusions

Our stage 1 application, the subject of this report, was submitted following the success of our application for an Accelerated Development Award. The purpose of the Accelerated Development Award was to provide core resource to research teams for 12 months to develop all aspects required to plan for a platform trial that is complex in design and delivery. This enabled us to accelerate completion of a master protocol, agreed by parent and patient groups, clinicians, and NHS/academic/industry partners, for a precision-medicine platform trial to test the efficacy of interventions in very preterm neonates. We were able to establish teams and collaborations to develop novel plans to conduct and test confirmatory mechanistic hypotheses; advance generalisable learning around platform study design, UK and international regulation; and undertake best practice in relation to parent/patient/clinician/industry involvement.

The stage 1 application deadline was 8 months into the 12-year Accelerated Development Award. One challenge experienced by this early timeline was with regard to the development of our video animation that we coproduced with parents and patients to a very high quality using a company with expertise in communicating health- and research-related information. We required this early to be able to use it to engage with the community, but without a final decision, major revisions and redevelopment were likely.

We included a collaboration with Australian units. The international working is beneficial as it would have enabled us to complete recruitment and achieve patient benefit earlier and increase generalisability. Conversely, international collaboration is complicated by different data collection processes, regulatory requirements, and need to secure in-country funding for recruitment and data collection. The curtailed timeline rendered us unable to complete this work within this accelerator award.

Additional information

CRediT contribution statement

Neena Modi (https://orcid.org/0000-0002-2093-0681): Conceptualisation (lead), Methodology (equal), Formal analysis (supporting), Investigation (lead), Resources (equal), Writing (lead), Project administration (lead), Funding acquisition (lead).

Mohammad Chehrazi (https://orcid.org/0000-0003-1770-4170): Methodology (equal), Formal analysis (lead), Writing (supporting).

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Alan Boyd (https://orcid.org/0000-0002-2716-3120): Industry liaison (lead), Writing (supporting).

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Ju-Lee Oei (https://orcid.org/0000-0002-7799-3771): Methodology (Australia/New Zealand lead), Writing (supporting), Project administration (equal).

Susan Ozanne (https://orcid.org/0000-0001-8753-5144): Mechanistic studies (equal), Writing (supporting).

Kylie Pussell (https://orcid.org/0009-0008-4183-2424): Patient–public involvement and engagement (Australia) (equal), Writing (supporting).

Sabita Uthaya (https://orcid.org/0000-0002-6112-2277): Conceptualisation (supporting), Methodology (supporting), Writing (supporting).

Hilary Wong (https://orcid.org/0000-0003-4597-1794): Methodology (supporting), Writing (supporting).

Victoria Cornelius (https://orcid.org/0000-0002-0080-1065): Conceptualisation (supporting), Methodology (lead), Resources (equal), Writing (equal), Funding acquisition (equal).

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Data-sharing statement

No new data have been collected during this study. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

No ethics approval was sought as this was an accelerator award to develop collaborations and undertake the work needed to prepare and design the study.

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/LMHT3521.

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About this article

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List of abbreviations

APAN	Adult Preemie Advocacy Network
CSD	clinically significant difference
EOP	encephalopathy of prematurity
HDR UK	Health Data Research UK
MCID	minimum clinically important difference
MRI	magnetic resonance imaging
NEC	necrotising enterocolitis

NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database
OMM	own mother's milk
PHDM	pasteurised human donor milk
PMA	postmenstrual age
RCT	randomised controlled trial
RD	risk difference
RR	risk ratio
SD	standard deviation

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Appendix 1

Simulation study graphical results

Figures 5–8 illustrate the criteria used to find the optimal triggers for posterior probability and test whether the proposed scenarios fulfil the desired criteria for type I and II errors. *Figures 5–7* show the proportion of futile and successful trials for 3%, 5% and null scenarios. *Figure 8* demonstrates the distribution of posterior probability of success for the 3% superiority scenario over control, across precision-medicine factor strata. This is the probability that response is greater than control by the CSD. It revealed that it was highly likely the trials simulated from this scenario would identify detectable effects based on the pre-specified triggers.

Results are shown by precision-medicine factors: Mlte25 = males < 25 weeks; Flte25 = females < 25 weeks; M26to28 = males ≥ 26 weeks and < 28 weeks; F26to28 = females ≥ 26 weeks and < 28 weeks.

The *y*-axes show both the time (weeks) taken to stop early and the proportion of simulated trials stopped by each precision-medicine factor. The green bars in *Figure 5* show the proportion of early stopping for success for the null scenario and should be compared with values on the left *y*-axis. The higher the bar, the higher the type I error. This figure reveals that the type I errors for the trial settings, including the triggers and thresholds, are quite small and meet desirable criteria for simulated trials. The boxes inside the figure show the distribution of the time taken to stop early for success. The simulated studies would be stopped at least after 60 weeks and just before week 84. It is also revealed that the median of stopping for success for a null scenario is approximately 100 weeks after first randomisation, which means it is unlikely the trial would stop for success over the first 2 years of the study if there was not really any treatment effect. *Figures 6* and *7* are interpreted in the same way and illustrate the time taken to stop early (boxes) and the proportion of stopping for futility (green bars) for 3% and 5% scenarios, respectively.

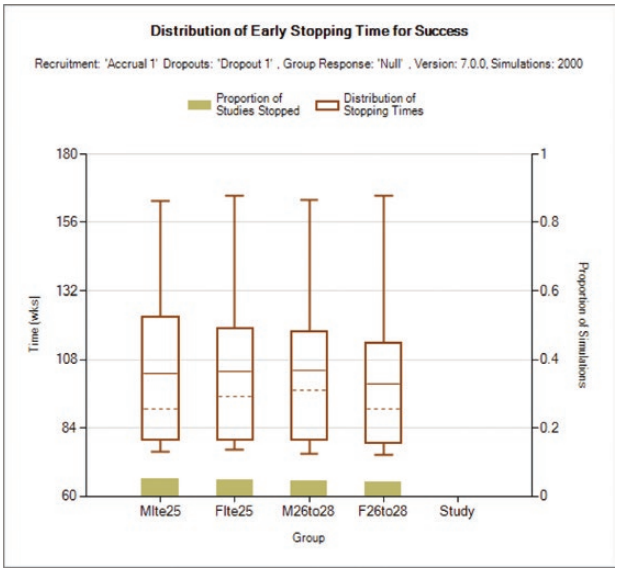

FIGURE 5 The proportion of early stopping for success and distribution of stopping time for the null scenario which assumed no treatment effect across the precision-medicine factor strata.

FIGURE 6 The proportion of early stopping for futility and distribution of stopping time for 5% superiority over control scenario which assumed at least 5% superiority over control in treatment effect across the precision-medicine factor strata.

FIGURE 7 The proportion of early stopping for futility and distribution of stopping time for 3% scenario which assumed at least 3% superiority over control in treatment effect across the precision-medicine factor strata.

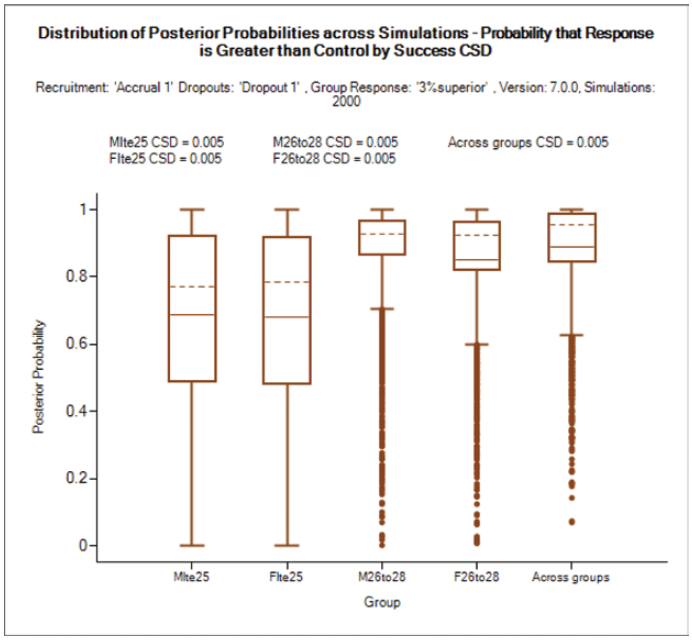

FIGURE 8 The distribution of posterior probability of success across simulations for the 3% scenario which assumed at least 3% superiority over control in treatment effect across the precision-medicine factor strata.