COLLABORATE

Improving newborn care together

Randomisation link: OpenClinica

https://auth.openclinica.io/auth/realms/imperial/protocol/openid-connect/auth?response_type=code&client_id=bridge&redirect_uri=https%3A%2F%2Fimperial.openclinica.io%2FOpenClinica%2Fsso%2Flogin&state=9021ca7d-b3de-4b2f-be1d-6de4aa65a96c&login=true&scope=openid

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OpenClinica Training: https://www.imperial.ac.uk/clinical-trials-unit/clinical-data-systems/cds-openclinica/training-openclinica-40/

The code is CDSTraining_123

Short summary:

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

Study objectives:

Randomised study primary objectives

- To assess, in babies born **<29 weeks gestation**, the efficacy of **pasteurised Human Donor Milk** (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 necrotising enterocolitis (NEC)" (primary outcome), language and cognitive development at age 2-years, and other outcomes
- To assess, in babies born **<29 weeks gestation**, the efficacy of **routine cow-milk based protein-carbohydrate fortification** of human milk feeds (Own Mother's Milk

and pHDM) compared with **no routine fortification** on "survival to 34 weeks postmenstrual age without surgical necrotising enterocolitis (NEC)" (primary outcome), language and cognitive development at age 2-years, and other outcomes

Mechanistic objective (sub-study led by Professor James Boardman, University of Edinburgh)

- To determine if **pHDM** and **Preterm Formula** exert **different effects on neurodevelopment** through the mechanism of **altered cerebral white matter** microstructure (sub-study)

NHS Value objective (led by Professor Ramon Luengo-Fernandez, University of Oxford)

- To establish if the **additional cost of pHDM to the NHS is justified** through a reduction in NEC

INCLUSION/EXCLUSION CRITERIA

Randomisation 1

Inclusion

- Born <29 weeks gestation
- No condition precluding enteral feeding
- Maternal intention to express breast milk
- Parent/guardian verbal consent

Exclusion

- Baby has already received pHDM or Preterm Formula

Randomisation 2

Inclusion

- Born <29 weeks gestation
- No condition precluding enteral feeding
- Maternal intention to express breast milk
- Parent/guardian verbal consent

Exclusion

- Baby has already received Fortifier

Mechanistic study

Inclusion

- Participants in randomisation 1 recruited at the Royal Infirmary of Edinburgh
- Parent/guardian written consent

Exclusion

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

Primary

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
- Medical NEC
- Age in days to achieve an enteral intake of 150 ml/kg/day
- Treated retinopathy of prematurity
- Severe brain injury
- Any diagnosis of milk-curd obstruction

- Length of neonatal unit stay
- Number of episodes of bacterial or fungal bloodstream infection
- Number of episodes of bacterial or fungal cerebrospinal fluid infection
- Number of episodes of bacterial or fungal urinary tract infection
- Number of days of antibiotic treatment
- Number of days on parenteral nutrition
- Number of days nil by mouth
- Weight, length, and head circumference Z-scores
- Change from birth in Z-scores for weight, length, and head circumference
- Any breast feeding (suckling at breast)
- Exclusive breast feeding (suckling at breast)
- Receiving any expressed Own Mother's Milk
- Receiving exclusive expressed Own Mother's Milk
- Maximum serum urea, creatine, and alkaline phosphatase
- Health resource use

Assessed at neonatal unit discharge (or death) in babies with NEC surgery

- Drain insertion prior to surgery (yes/no)
- Diagnosis of short bowel syndrome (yes/no)
- Diagnosis of intestinal failure-associated liver disease (yes/no)
- Length of bowel resected (cm)
- Primary surgical procedure (ileostomy; colostomy; end-to-end anastomosis)
- Number of re-operations (excluding primary operation)
- **Assessed at age 2-years corrected for prematurity**
- Survival without moderate-severe cognitive-language impairment
- Survival
- Moderate-severe cognitive-language impairment
- Cognitive sub-score
- Language sub-score

- Gross motor function
- Hearing impairment
- Vision impairment

Timing:

Babies may participate in either or both randomisations; see Flow Chart, Appendix 1.

Randomisation 1 to pHDM or Preterm Formula, will occur when the attending 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 pHDM). By "fortification" we mean immediate or incremental increase to "full strength fortification" according to neonatal unit practice. We refer to "no routine fortification" because rescue fortification is permitted (refer to faltering growth section below)

Faltering growth:

Clinicians may consider discretionary use of fortifier in babies participating in randomisation 2 if the following conditions apply:

- If after 2 weeks of reaching a human milk volume of at least 120 ml/kg/d, and higher volumes have not been tolerated, a baby shows a 3 "marked-centile" downward crossing (approximately 1.4-2.0 *z* score change from birthweight) on the UK Neonatal and Infant Close Monitoring growth chart
- The blood urea is below 1.5 mmol/l indicating no protein excess and likely protein deficiency
- Chronic sodium depletion has been excluded: chronic sodium depletion will manifest by a slowing of weight gain despite a human milk of around 180ml/kg/day even though the serum sodium concentration will be normal; administration of an initial supplement of 2 mmol/kg/day in divided doses will result in an immediate increase in weight
- No severe intercurrent illness

Clinicians considering rescue fortification are advised to discuss this with the clinical CI or delegate. Rescue fortification will be documented in the eCRF and factored into analyses.

Adverse Event (AE):

An AE is any untoward medical occurrence in a clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), whether or not considered related to the trial protocol.

Serious Adverse Event (SAE):

An SAE is defined as any event that

- Results in death
- Is life-threatening*
- Requires prolongation of hospitalisation**
- Results in persistent or significant disability or incapacity

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** "Hospitalisation" means any extension of hospitalisation; it does not apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Adverse Reaction (AR):

All untoward and unintended responses to the study intervention. All AE judged by either the reporting investigator or the sponsor as having reasonable causal relationship to the study intervention qualify as AR.

Serious Adverse Reaction (SAR):

A SAR is defined as a SAE that is judged to be related to any study intervention given to the participant.

-Death, Medical and surgical NEC are expected SARs, will be reported and monitored during the study by the data monitoring and ethics committee.

Reporting of unexpected SAR will be performed through the eCRF. Unexpected SAR should be reported within 24 hours of the site study team becoming aware of the event as serious, unexpected and related. SAR will be reported to the Sponsor's delegate (ICTU). Further details can be found in the safety reporting manual.