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Hummingbird study

A protocol for a randomised controlled trial exploring human milk, nutrition, growth, and breastfeeding rates at discharge: The Hummingbird study

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ABSTRACT

Introduction

Mother's own breast milk (MOM) is the optimal nutrition for preterm infants as it reduces the incidence of key neonatal morbidities and improves long-term outcomes. However, MOM shortfall is common and either preterm formula (PF) or pasteurised donor human milk (DHM) may be used, although practice varies widely. Limited data suggest that the use of DHM may impact on maternal beliefs and behaviours and may therefore impact on breastfeeding rates. The aim of this pilot study is to determine if the duration of DHM exposure impacts on breastfeeding rates, and maternal breastfeeding self-efficacy.

Methods and analysis

The Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge (Hummingbird) study is a feasibility and pilot, non-blinded, randomised controlled trial (RCT) with a contemporaneous qualitative evaluation. Babies born at less than 33 weeks gestation or with birth weight <1500 grams whose mothers intend to provide MOM are randomly assigned to either control arm (DHM used to make up shortfall until full feeds, then PF used thereafter) or intervention arm (DHM used to make up shortfall until 36 weeks corrected age or discharge if sooner). The primary outcome is breastfeeding rates at discharge. Secondary outcomes include growth, key neonatal morbidities, length of stay, breastfeeding self-efficacy and postnatal depression using validated questionnaires. Qualitative interviews using a topic guide will explore perceptions around use of DHM and will be analysed using thematic analysis.

Ethics approval and dissemination

Nottingham 2 Research Ethics Committee granted approval for HUMMINGBIRD Study on 6th April 2021 (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. Results will be disseminated in peer-reviewed journals.

Trial registration: Trial was registered prospectively on 4th May 2021 (ISRCTN 57339063).

INTRODUCTION

Approximately 60,000 babies are born prematurely (<37 weeks) in the UK each year. While most are born late preterm (34 -37 weeks), around 10,000 babies are born very preterm (<32 weeks' gestation) (1). Preterm babies often need neonatal intensive care and prolonged hospital stay. While survival rates of extremely preterm (<28 weeks) infants have notably improved over the past two decades, death is still relatively common (2), with late onset sepsis (LOS) and necrotising enterocolitis (NEC) being the most prevalent (3). Preterm infants are at significant risk of long-term complications such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and cognitive impairment (4). Nutritional management impacts on short and long-term neonatal outcomes (5) but remains challenging as macronutrient intakes can sometimes be hard to meet. (6).

Mother's own milk

Mother's own milk (MOM) provides the basis of the optimal diet for preterm babies (7) due to the composition of key proteins and lipids, but also because it provides hormones, enzymes, growth factors and other unique and dyad-specific bioactive nutrients such as

human milk oligosaccharides (HMOs) which facilitate early colonisation of the gut. Use of MOM is associated with decreased risk of major neonatal morbidities such as NEC, LOS, ROP or BPD (8-11), and this effect is dose-responsive (12). Whilst an exclusive MOM diet has been associated with slower growth in very low birth weight (VLBW) infants compared to growth with PF use (13, 14), cognitive, cardiac and metabolic outcomes are better (15-17).

Challenges of expressing MOM and breastfeeding in NICU

Despite strong evidence about the benefits of MOM, low breastfeeding rates remain a major health concern. Over 90% of mothers now provide at least some breastmilk after preterm delivery, but breastfeeding rates at discharge for preterm infants vary considerably from 19-70% across Europe (18). In addition to challenges many women experience when breastfeeding, mothers of preterm babies may also be unwell, they must cope with the stress of having a preterm, often sick infant who is physically separated from them from birth, and they need to maintain breastmilk expression for several weeks. Furthermore, the initiation of lactogenesis is often impaired after preterm birth (19).

In view of these challenges, effective support and counselling for mothers who express milk in the NICU is vital. Despite targeted support, shortfall of MOM is common in neonatal intensive care units (NICU)s with more than 80% of infants requiring additional milk at some point (1).

Donor Human Milk

The World Health Organisation, American Association for Pediatrics and European Society of Paediatric Gastroenterology, Hepatology and Nutrition recommend the use of donor human

milk (DHM) for feeding premature infants as a first alternative when there is a MOM shortfall (7, 20), despite the relatively lack of high-quality RCTs and heterogeneity of studies. A recent Cochrane review suggested that DHM may reduce risk of NEC compared to PF, with at least 33 infants needing to receive DHM to prevent one NEC case. The data do not support a reduction in mortality or longer-term neurodevelopmental benefits, and many studies were noted to have been conducted more than 20 years ago. (21). Zipitis et al. demonstrated differences in DHM use amongst UK NICUs (22), with some only providing DHM for the first 10 days of a baby's life whereas other units use DHM until closer to discharge. Battersby et al. showed that variation between NICUs is not related to the presence of a local milk bank and is most likely linked to uncertainties around DHM use (23). One key uncertainty is whether DHM affects duration of breastmilk expression or breastfeeding. A systematic review of 10 studies showed that DHM may have a positive impact on *any* breastfeeding but does not appear to affect rates of *exclusive* breastfeeding on discharge (24). A large observational study analysing DHM availability in 56 NICUs in the USA showed positive effects on breastfeeding in NICUs where a DHM programme was implemented, along with a decrease in NEC rate (25). A historical cohort comparison study pre- and post-DHM introduction demonstrated increased breastfeeding at discharge and increased consumption of MOM (26). In contrast, another single-centre retrospective study showed that MOM provision decreased over a two-year period following the implementation of a donor milk program where preterm infants consumed less MOM in the first 14 days in the post-DHM cohort. (27). Esquerra-Zwiers et al. showed similarly reduced exclusive MOM use in the first two weeks of life with DHM availability compared to a pre-DHM cohort. However, in these studies enteral feeds were commenced earlier, and infants were exposed to formula later in life in after DHM introduction (28). More recently,

Mondkar et al. showed that DHM use in addition to optimising breastfeeding support and kangaroo care led to improved exclusive human milk feeding (29).To date, no RCT has studied the relationship between donor milk availability and breastfeeding at hospital discharge.

Preterm formula

The composition of PF is designed to meet the high nutritional demands of the preterm infant. This has resulted in improved weight gain, linear growth, and head growth of preterm infants (21). However, no RCTs have shown improved long-term growth or neurodevelopmental outcomes compared to use of MOM or DHM (21, 30). PF may provide a more consistent delivery of macro- and micro-nutrients but lacks non-nutritive content, so called bionutrients, which might be key in reducing disease (e.g. NEC), establishing diverse gut microbiota and improving long-term outcomes (31, 32). The cost of PF (around £5 per litre) is almost 30-fold lower than the cost of DHM (between £125-150 per litre). However, if supplemental DHM feeding prevented NEC, total costs for hospitalisation would favour DHM compared to PF use (33).

Summary of key issues: donor human milk as a 'complex intervention'

In summary, MOM is the optimal source of nutrition for preterm infants. Despite this evidence, breastfeeding rates in the UK are amongst the lowest in the world (34), and breastfeeding rates in the North East of England are some of the lowest in the UK (35). This is also reflected in breastmilk feeding of premature infants. Currently, around 90-95% of

mothers in the North East start expression of breastmilk for their preterm baby, but only 35% are still providing breastmilk at discharge compared to the national average of 60% (35). Improving availability of MOM in NICUs is crucial to reducing key neonatal morbidities. The use of DHM is increasing in most UK neonatal units and is recommended by ESPGHAN when there is a shortfall of mother's own milk, largely because meta-analysis suggests a lower rate of NEC (21). However, because DHM also affects growth, which may in turn be associated with longer term brain and metabolic outcomes, the optimal strategy for improving lifelong health remains uncertain. Observational data show that availability of DHM impacts on breastmilk expression and breastfeeding duration demonstrating that DHM affects beliefs and behaviours of mothers, healthcare staff or perhaps both, and DHM is therefore a 'complex intervention'. Complex interventions in healthcare impact on biology (i.e. health and disease), behaviour and belief (e.g., breastfeeding rates). They may have multiple relevant outcomes and mechanistic causal pathways; and may be affected by context e.g. NICUs with differing background rates of NEC or breastfeeding. There is often long lag time between intervention and outcome (metabolic and cognitive outcomes in adulthood) (36).

Provision of DHM may be the best example of a complex intervention in neonatal medicine, and uncertainties around the optimal strategy are unlikely to be resolved with a single RCT. However, this trial could lay foundation for further trials to investigate the optimal implementation and use of DHM (Figure 1).

METHODS AND ANALYSIS

The HUMMINGBIRD study is a randomised open-label controlled trial set in two tertiary neonatal units in the North East of England. It is designed to compare two different nutritional strategies which use DHM to make up any shortfall in MOM for preterm infants (Table 1)

Population

Infants born before 33 completed weeks of gestation or with a birth weight of less than 1500 g whose mothers intend to express breastmilk after delivery and are willing to accept DHM are eligible. Only infants with written informed consent from parents and randomised within seven days of birth can be included. Infants who were born with major congenital or life-threatening abnormalities or who were exposed to formula milk prior randomisation are excluded.

Intervention: DHM duration

This study aims to assess the impact on breastfeeding at discharge, therefore infants in the intervention group will only continue to receive DHM if their mother is still expressing breastmilk. Where the infant has not received any mother's own breastmilk for one week, or where the mother has told clinical staff she is no longer expressing, the use of DHM will be discontinued and the baby will receive a standard formula milk designed for preterm infants.

Control: DHM duration

Full feeds are defined as a volume of 150 ml/kg/day tolerated for 48 hours. If a shortfall of MOM occurs beyond this point, infants in the control group will receive preterm formula milk.

Randomisation

Infants are randomised with a secured, password protected web-based randomisation tool using a minimisation algorithm (www.sealedenvelope.com) that incorporates the following variables: gestation (<28 weeks yes/no), and twin/triplet status (yes/no). Twins, triplets, and higher multiples are co-randomised to the same trial arm.

Study Outcomes

Primary outcome

Any breastfeeding, or mother still actively expressing milk, at 36 weeks corrected age or discharge if this is earlier.

Secondary outcomes – growth, feeding and neonatal outcomes

1. Growth – weekly weight, length and head circumference, absolute changes (g/kg/day and mm/week) and change in standard deviation score
2. Neonatal morbidities:
    a. Episodes of confirmed NEC Bell stage 2 or greater
    b. Late onset sepsis confirmed and clinically suspected according to existing case definitions (37)
    c. Chronic lung disease (oxygen requirement or respiratory support at 36 weeks)
    d. Retinopathy of prematurity (ROP)
    e. Intraventricular haemorrhage and/or cystic periventricular leukomalacia

3. Days of intensive, high and low dependency care (38); corrected age at discharge, total length of stay (days)
4. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks
5. Age at starting breastmilk fortifier and number of days when fortifier is provided
6. Type of feeding at discharge (direct breast feeding, tube feeding etc.)
7. Type of milk and feeding at 6- and 12-weeks post discharge

Secondary outcomes – maternal questionnaires and qualitative data

A validated questionnaire, Breastfeeding Self-Efficacy Scale – Short Form (BSES-SF) adapted for preterm infants (39), is given to mothers at two time points – around 10 days postnatal age and again at 35-36 weeks corrected age or prior to discharge if sooner. The Edinburgh Postnatal Depression Scale (EPDS) questionnaire will also administered to mothers around day 10 postpartum (40). BSES-SF and EPDS scores will serve as a tool to stratify mothers into two groups (scores in the bottom and top quartile of scores). This will be used as a guide to ensure that both groups will be represented in the subset of interviewed mothers.

Qualitative interviews with mothers will be conducted to explore perceptions around donor milk use and barriers and facilitators to expressing MOM. These one-to-one, in-person semi-structured interviews will be audio-recorded and transcribed. We estimate that 15-20 interviews will be recorded although final number of interviews will be determined by thematic saturation generated through interpretation of data (41).

Hypothesis, sample size and power

We hypothesise that longer access to DHM (intervention arm) will improve the rate of breastfeeding at discharge from the current rate of 35% to the UK national average of 60%. Fifty-eight infants per trial group will be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive, at least 130 infants need to be recruited to complete the trial. We estimate that up to 20% of infants may be discharged before 36 weeks corrected age to a local neonatal unit that does not have continued access to DHM. We will therefore need to recruit between 130 and 156 infants in order for the study to be powered at 80%, and we estimate this will take 18-24 months recruitment.

Analysis

Data will be analysed using an intention-to-treat approach, but additional analysis will be performed only using breastfeeding outcome data for those completing the study (i.e., excluding transfers) and the first baby from a multiple pregnancy enrolled. Categorical data will be presented as counts and frequencies and will be compared using chi squared or Fisher exact test as appropriate. Continuous data will be presented as mean (SD) or median (IQR) and the Shapiro-Wilk test will be used to test the normality of the data. Group differences in continuous data will be compared using Student's t-test or Mann-Whitney U test for normally and non-normally distributed data respectively. All tests will be performed two tailed and $p<0.05$ will be deemed statistically significant. Qualitative data will be analysed using reflexive thematic analysis (42).

What is already known on this topic:

The benefits of MOM for preterm infants are well recognised but uncertainties remain around the optimal strategy for DHM use, especially whether it impacts on breastfeeding success. DHM is a complex intervention as it impacts on infant health and disease as well as maternal and healthcare staff behaviours and beliefs.

What this study adds:

To our knowledge, HUMMINGBIRD is the first RCT to investigate DHM as a complex intervention.

How this study might affect research, practice or policy:

A single RCT of a complex intervention is unlikely to resolve all uncertainties. In this respect, current systematic reviews of the role of DHM may be of low certainty and do not clearly identify the optimal strategy. Studies incorporating quantitative and qualitative methods may better elucidate the role of DHM in NICUs. HUMMINGBIRD may help optimise the design of future studies in larger scale.

ETHICS APPROVAL AND DISSEMINATION

Nottingham 2 Research Ethics Committee granted approval for HUMMINGBIRD Study on 6th April 2021 (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. A trial steering committee including independent members and parents will oversee trial conduct and progress. The trial is compliant with the UNICEF Baby Friendly Initiative. Results will be disseminated in peer-reviewed journals.

COMPETING INTERESTS

NS is the cofounder of the Human Milk Foundation, a UK charity that provides donor human milk. NE and JB report research grants paid to their institution from National Institutes for Health Research, Action Medical Research, Prolacta Biosciences US, Danone Early Life Nutrition and NeoKare but received no personal fee, and have no other financial conflicts related to industry funding. NE reports lecture honoraria from Nestle Nutrition Institute, and Astarte Medical.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors and was supported using internal departmental funds.

AUTHORS' CONTRIBUTIONS

NE had original idea for Hummingbird trial after discussions with NS and played a key role in developing the protocol. JB contributed to study design and protocol development. All authors contributed to the writing and review of this paper and gave final approval for its submission.

ACKNOWLEDGMENTS

Not applicable.

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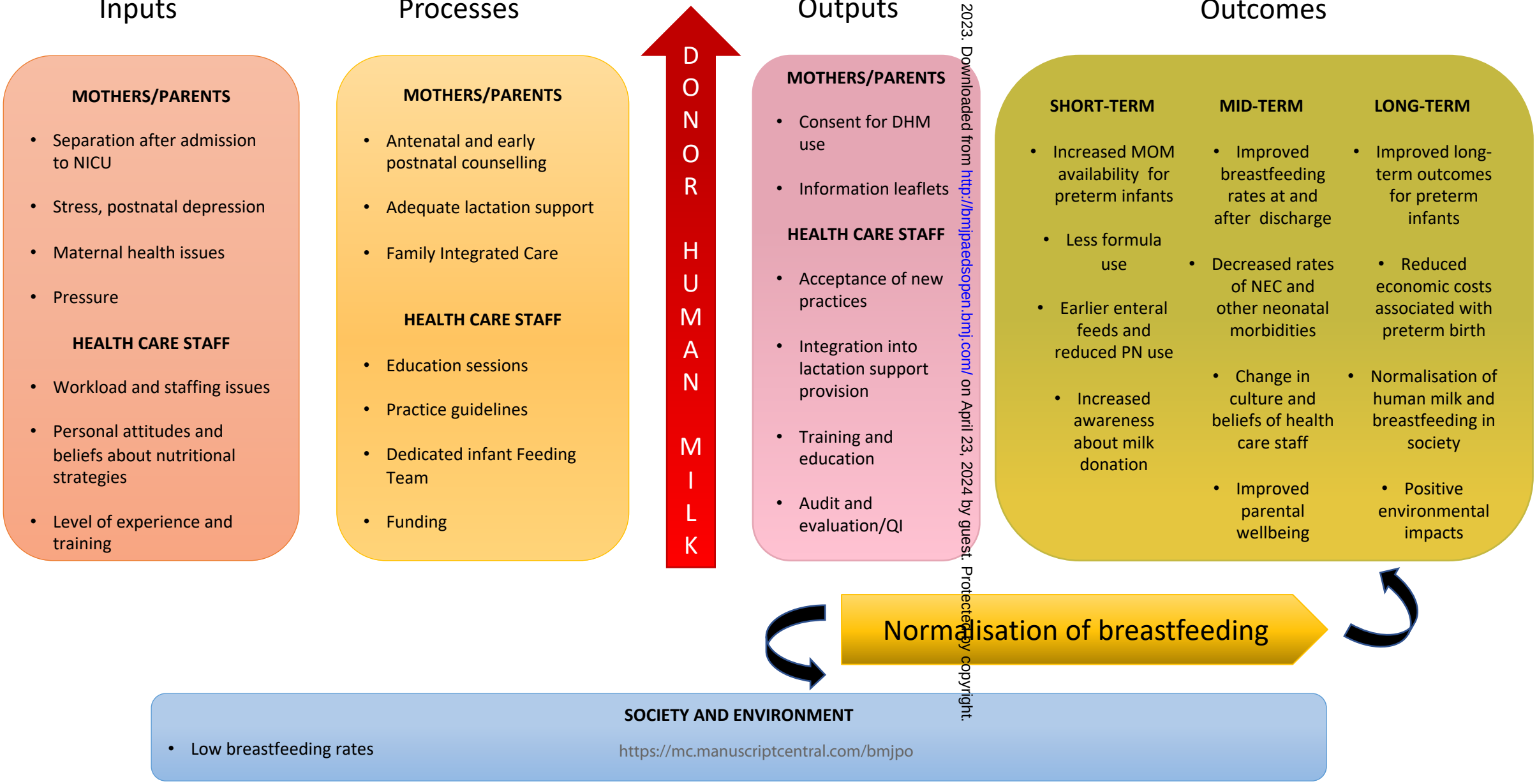

Setting	Tertiary level NICUs in North East England
Population	Preterm infants <33 weeks or with a birth weight <1500g admitted in the first seven days of life
Intervention	Use of DHM to make up any shortfall in MOM until 36 weeks corrected age (or discharge if this comes earlier)
Control	Use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours)
Design	Randomised open-label controlled trial
Timeframe	Until 36 weeks corrected gestation or hospital discharge if earlier

Table 1. Summary of study methods

Human MIlk, Nutrition, Growth, and Breastfeeding Rates at Discharge: The Hummingbird Study

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Sponsor: Newcastle Hospitals NHS Foundation Trust

IRAS Project ID: 281071

Sponsor Protocol number: NuTH 09735

Trial registration number: ISRCTN

REC reference number:

Investigator team

Dr Kristina Chmelova	Trust doctor in Neonatal Medicine, Newcastle Hospitals
Dr Janet Berrington	Consultant Neonatal Paediatrician, Newcastle Hospitals
Professor Judith Rankin	Professor of Maternal and Child Health, Newcastle University
Ms Maria Douglass	Infant feeding lead, Newcastle Hospitals
Dr Stefan Zalewski	Consultant Neonatal Paediatrician, Newcastle Hospitals
Dr Claire Granger	Research Fellow in Neonatal Medicine, Newcastle Hospitals

Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

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Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

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Trial Steering Committee (TSC)

Name	Role
TBC	Independent chair
Dr Nicholas Embleton	Chief Investigator
TBC	Parent
TBC	BFI/Advocacy rep
Maria Douglass	Breast feeding support nurse
Professor Judith Rankin	Co-investigator
Dr Janet Berrington	Co-investigator
Dr Stefan Zalewski	Co-investigator

Study proposal summary

This is the protocol proposal for a single site, non-blinded, randomised controlled trial exploring two currently used dietary regimes in preterm infants. The dietary regimes involve fully supporting mothers to provide their own expressed breast milk and using donor human milk to make up any shortfall in breastmilk supply. The primary outcome is maternal breastfeeding rates at discharge. Mothers of infants on ward 35 neonatal unit at the Royal Victoria Infirmary will be approached by clinical team members, and infants will be enrolled after signed informed consent. Infants do not undergo any additional interventions or tests, and all data used is routinely collected. Mothers will complete short questionnaires on two occasions and a subset invited to take part in qualitative interviews. The study intervention finishes at hospital discharge, but two telephone calls post-discharge will be made to ascertain duration of any prolonged breastfeeding

Title (Acronym)	Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge: **The Hummingbird Study**
Study centre	Ward 35, Newcastle Royal Victoria Infirmary. Additional sites may be added

Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

Study objectives	To compare two dietary regimes that both use mother's own breastmilk and donor human milk to make up any volume shortfall
Study design	Randomised open label, controlled trial
Study population	Inclusion criteria • Preterm infants born <33 completed weeks of gestation or <1500g birthweight • Admitted to neonatal unit in first week of life • Written informed consent from parents • Maternal intention to provide breastmilk after birth Exclusion criteria • Parents unwilling to accept donor human milk • Major congenital or life-threatening abnormalities • Inability to randomise within 7 days of birth • Exposure to formula milk product prior to randomisation
Interventions	Donor human milk until full milk feeds established (control) compared to donor human milk until discharge for as long as the mother is still providing her own milk
Target number of patients	130-160 infants
Randomisation	Minimisation incorporating the following variables: gestation (<28 weeks yes/no), and twin/triplet status (yes/no) Secured, password protected web-based randomisation using minimisation algorithm (www.sealedenvelope.com or similar)
Primary outcomes	Breastfeeding at hospital discharge or 36 weeks corrected age
Secondary outcomes	Feed and growth-related outcomes Neonatal morbidities and clinical outcomes Maternal breast-feeding self-efficacy & postnatal depression scores Thematic analysis of qualitative interviews (subset)
Duration of trial intervention	36 weeks postmenstrual age or hospital discharge (which ever earlier)
Duration of study	Recruitment period: 18 months Total trial duration: 21 months

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End of Trial	Discharge from neonatal unit at Newcastle
Safety assessments	Routine assessments until discharge from Ward 35 Neonatal Unit Safety tracking during hospitalisation

Introduction

Around 10% of all births are premature, but whilst the majority do not require specialist medical treatment, those born very preterm (<32 weeks gestation) require prolonged hospital stay including intensive care. Survival in these infants has increased dramatically in recent years, but death is still common (~10% overall) as are the consequences of life-long physical and cognitive impairment.[1] In the UK around 10,000 premature infants are born every year, representing an annual cost to the NHS of ~£3 billion.[2]

The commonest cause of death or serious illness in preterm infants after the first few days are gut complications such as necrotising enterocolitis (NEC) or septicaemia.[3] Morbidity and mortality is lower in infants who receive mother's own expressed breastmilk (MOM) but >80% still require additional milk supplementation.[4] This is because there is often a 'shortfall' in maternal milk supply either due to inadequate lactation, or because mothers choose to discontinue expressing breastmilk before infants' are discharged home. Over 90% of mother's now provide at least some breastmilk, but breastfeeding rates at discharge vary considerably from 30-80% depending on hospital.[5] Low rates of breastfeeding are a major health concern, as there is strong evidence that breastfeeding throughout infancy is beneficial for cognitive and metabolic outcomes (e.g. obesity, high blood pressure etc.) in childhood and throughout the life-course.[6,7]

Use of donor human milk (DHM)

When there is a shortfall in MOM supply, an alternative milk is needed, which is either formula milk, or pasteurised, donated, human milk (DHM).[6,8] DHM is provided from one of ~12 donor milk banks in the UK which collect milk from UK donors. DHM must be tested, pasteurised, frozen and transported to hospitals for use. Because of this DHM is much more expensive (£150/litre) than formula milk (£5/litre). Studies also suggest that DHM may be less beneficial than mother's own milk at reducing neonatal disease, and strong support for mothers to provide their own milk is universally accepted.[9]

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DHM has been widely used for >30 years in the NHS, but there is no national system for supply, and use varies dramatically: some clinical networks do not use it at all, whereas others provide it routinely to all preterm infants.[10] No trial has ever been powered to determine a realistic reduction on rates of necrotising enterocolitis (NEC) or sepsis and such a trial would probably need to recruit at least 2500 infants.[4] There have been no large UK trials of donor human milk in preterm infants ever, and no nationally agreed, evidenced based guidelines for use exist.[10] The only two, recent, moderately sized (300-400 infants) RCTs showed differing effects. A Canadian trial showed no improvement on the primary outcome of cognitive outcome in infancy, although NEC was lower in a secondary analysis; however, there was no impact on survival.[11,12] A larger Dutch trial showed no effect on death, NEC or sepsis (combined primary outcome) although DHM was only provided for the first 10 days of life.[13] Our current Cochrane meta-analysis concluded that there is no evidence for a reduction in death, or any long-term benefits, but whilst NEC may be lower around 33 infants would need to receive DHM to prevent one case.[4]

In the last 20 years we identified only 5 RCTs including just 1200 infants in total, of which only one study was conducted in Europe. No trials included a qualitative analysis and economic analyses was only conducted in one trial which showed no difference in costs to 18 months age. In the UK, the healthcare costs of DHM need to be considered in order to determine which infants should receive DHM. Inconsistent observational data suggest an impact of donor milk on breast feeding rates, but no trials reported the impact on continued breastfeeding at discharge.[14] Our systematic review concluded that whilst there may be an impact on breastfeeding at discharge where DHM is used (perhaps by creating a more positive culture of breastfeeding), the effect was weak and inconsistent.[15]

Whilst all neonatal units now strive to support mothers to provide breastmilk, proponents of DHM argue that it's use creates a more positive effect on mother's, as well as health professional belief and culture, will result in longer duration of breastmilk expression, and ultimately duration of breast-feeding. However, whilst there are observational data, this has never been tested in well-designed RCTs, and a recent systematic review determined the overall impact was equivocal.[15] Nevertheless, increasing numbers of women, and support groups, now advocate for universal use of DHM in vulnerable infants throughout hospital stay, despite the lack of conclusive data and high-quality health economic evaluation.[16–18]

Current practice of DHM in the UK

Despite the widespread use of DHM, indications and practical use varies widely between Neonatal Intensive Care Units (NICUs) and hospitals. Some NICUs restrict use to only those infants born <28 weeks whereas others provide to all infants <32-34 weeks or <1500g. Some hospitals also use DHM for term born infants with cardiac and gut conditions, and in some situations, parents have asked for DHM to be used in term born infants where maternal supply is inadequate. In the first few days when milk feeds are established in preterm infants only relatively small DHM volumes are required, but volume (and therefore costs) increase as the infant grows. Clinical practice in NICUs in the UK varies widely.[10,19,20] Some NICUs only use DHM until full milk feeds have been established. This is because most key events linked to feeding (sepsis, NEC and other severe illness) occur in the first 10 days. However, other units will use DHM until closer to discharge because some clinicians feel this is more likely to support longer term breast feeding.

A further challenge arises because human breast milk alone will not meet the nutrient requirements for preterm infants.[21] To meet the higher nutrient requirements of preterm infants, commercially produced breast-milk-fortifiers (BMF) are added to mothers' own milk or donor milk. Although human milk-based fortifiers are available these are not widely used outside the USA and are very expensive.[22] BMF is therefore produced from cow's milk and is therefore a similar product to cow's milk infant formula. Many clinicians feel that rather than adding BMF to donor milk it would be preferable to use a milk formula.[20] This is because growth is slower in infants receiving DHM, and there are concerns that slow early growth may increase the risk of other problems, including worse cognitive outcomes. In addition, the continued use of DHM after full feeds are established in a typical preterm infant at 28 weeks born weighing 1000g, would cost around £1000-2000 more where the infant receives all DHM compared to infants receiving formula (in the situation where mothers do not provide any breastmilk).

Summary of key issues

In summary, use of donor human milk is commonplace in most UK neonatal units and despite the lack of a conclusive evidence base seems likely to remain a common choice for many clinicians where there is a shortfall in mothers' own milk. Most parents appear to favour use of DHM, and DHM is also strongly supported by advocacy groups including the WHO and UNICEF. There is no consistent approach to the use of DHM once feeds are established, and growth is faster when formula is used. DHM is also more expensive compared to formula. DHM may improve breastfeeding rates at discharge, and/or improve maternal self-efficacy for breast feeding, but if there are no additional

benefits from more prolonged use then resources may be better spent elsewhere, for example by employing more lactation specialists to support mothers to provide their own milk.

Proposed study to explore impacts on breastfeeding

The Hummingbird study is designed to compare two clinical dietary approaches, both of which are routinely used in the UK, by comparing the use of DHM to make up any shortfall in MOM until full feeds (control) to that of using DHM for a longer duration up to the pre-discharge period (intervention).

- **Setting**: Tertiary level NICU on ward 35, Royal Victoria
- **Population**: preterm infants <33 weeks or <1500g admitted in the first 7 days of life
- **Intervention**: use of DHM to make up any shortfall in MOM until 35-36 weeks corrected age (or the initiation of breast feeding)
- **Control**: use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours) and use of preterm formula milk to make up shortfall thereafter
- **Primary outcome**: any breastfeeding at 36 weeks corrected age or hospital discharge if this is earlier. This outcome is also met if a mother is still actively expressing breastmilk which the infant receives wholly or in part via a bottle/
- **Study design**: non-blinded randomised controlled trial
- **Timeframe**: until 36 weeks corrected gestation or hospital discharge is earlier

Currently around 90-95% of our mother's start expression of breastmilk for their baby, but only 35% are still providing breastmilk at discharge compared to the national average of 60%.[5,23] The rate in the North East of England is around the lowest in the UK. Mothers who choose or are unable to continue providing MOM may do this at any point in time after they have started. Because this study is designed to impact on breastfeeding at discharge, infants in the intervention group will only continue to receive DHM if their mother is still continuing to provide breastmilk. Where the infant has not received any mother's own breastmilk for 1 week, or where the mother has told clinical staff she is no longer expressing, we will discontinue use of DHM, and the baby will receive a standard formula milk designed for preterm infants.

Secondary outcomes – growth and neonatal outcomes

We will collect a range of relevant common neonatal secondary outcomes:

1. Growth – weekly weight, length and head circumference, mid-arm/thigh where feasible, absolute changes (g/kg/day and mm/week) and change in standard deviation score
2. Episodes of NEC, sepsis - confirmed and clinically suspected according to existing nationally agreed case definitions
3. Chronic lung disease, Retinopathy of prematurity (ROP), Intraventricular haemorrhage, Cystic PVL etc.
4. Days of intensive, high and low dependency care; age at discharge, total length of stay
5. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks
6. Age at starting fortifier
7. Type of feeding at discharge (direct breast feeding, tube feeding etc.)

Secondary outcomes – breastfeeding self-efficacy and thematic analysis of interviews

We will use a mixed methods approach to determine maternal breastfeeding self-efficacy expression and conduct qualitative interviews in a subset of up to 20 mothers. We will use two short validated questionnaires – the Breast-feeding Self-efficacy Scale – Short form (BSES-SF)[24,25] and the Edinburgh Postnatal Depression Scale[26] - at two time points: between 5-10 days of age and again at 35-36wca or prior to discharge if sooner. These only take around 1-2 minutes to complete. We will use the BSES-SF scores to identify women in the top and bottom quartiles of scores and invite up to 10 women per trial group to take part in a qualitative tape-recorded interview. This will be transcribed and analysed using thematic analysis. We will develop a topic guide based on the questions on the BSE-SF and our experience (see appendix). Interviews will be conducted by a single member of the research team (KC) shortly before or after hospital discharge. We will seek consent to keep in touch with parents after discharge. We will also ask for consent to keep in telephone contact with mothers who are breastfeeding at discharge at 1-2 monthly intervals in order to simply ascertain duration of breastfeeding.

Sample size and Power

We hypothesise that prolonged use of DHM will improve the rate of breastfeeding at discharge from 35% to the UK national average of 60%. Fifty-eight infants per trial group would be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive we will need to recruit at least 130 infants who are still receiving care at the RVI at ~36 weeks corrected age (wca). We estimate that up to 20% of infants may be discharged before 36wca to a local hospital that does not have continued access to DHM. We will therefore need to recruit between 130 and 156 infants in order that we are powered to determine the primary outcome. The NICU on ward 35 admits ~160 babies every year <1500g or <33 weeks of whom we expected around 80% of infants

will be enrolled (based on previous RCTs we conducted). Therefore, we estimate we will need a 12-18 months recruitment period so we can enrol at least 130 infants who achieve the primary outcome. Twins and triplets will be co-randomised to the same trial arm. We will analyse the data for all infants using an intention-to-treat approach, but we will perform additional analysis only using breastfeeding outcome data for the first twin enrolled.

Funding

This trial will use dietary treatments already used in this way on the neonatal unit and collect routinely available electronic clinical data extracted from e-record and Badger neonatal database and inputted into an excel worksheet. There are no costs for use of questionnaires. Trial recruitment, consenting and interviews will be conducted by a member of clinical staff who has time available as part of daily activities (KC) supported by the neonatal research nurse. Costs for ISRCTN registration, printing, paperwork, tape recording, transcription, and travel costs for membership of the TSC will be met out of existing departmental research funds.

Trial registration, Ethics, HRA and risk burden

The trial will be registered on ISRCTN prior to opening. We will apply for HRA and REC approvals and apply for adoption onto the NIHR portfolio. There are no specific ethical issues with this trial, but we recognise the additional burden placed on parents by being asked to consider trial enrolment. There are no additional safety issues as part of the trial *per se*. Use of donor breastmilk could be associated with theoretical risks (although none have been documented) or inadvertent use of the 'wrong' milk, but donor milk is already used in routine practice and this trial does not increase the risk. No additional interventions or tests are applied to infants as part of the trial. The questionnaires do ask sensitive information but only members of the clinical team will see the responses and will already be aware of important family and mental health issues as part of routine family centred care on the neonatal unit. Where the mother wishes, we will use the questionnaire responses to provide further targeted support to help her. The trial is fully compliant with national recommendations and Baby Friendly Initiative (BFI) part of UNICEF.

Patient Public Involvement and importance to the NHS

We have discussed this study with parents on the neonatal unit, and other parents after discharge. Parents tell us that the risks and complication associated with feeding preterm infants, and the stress of being able to provide breastmilk for their infant are very important issues. In addition, the James Lind alliance (JLA) priority setting www.jla.nihr.ac.uk/priority-setting-partnerships/preterm-birth/top-10-priorities/ identifies feeding and nutrition as very important. Our study focuses on key JLA priorities (i) what is the optimum milk feeding strategy (ii) what type of support is most effective in improving

breastfeeding and will provide additional information relevant for a further 2 additional priorities (iii) how can infection be better prevented (iv) what interventions are most effective at preventing NEC. This trial is of major relevance to the NHS and studies interventions and outcomes highlighted in a recent top research priority setting in preterm infants.[27] Breastfeeding is a major national priority and is an intervention that has potential to benefit marginalised and poorly resourced groups. Breastfeeding support in the community is essential to continued successful breastfeeding but is recognised as being inadequate in many settings. NEC is a devastating condition, and half of the infants requiring surgery die or have long-term serious disability. Donor human milk is an important cost for the NHS, but the total costs of DHM even for a large NICU will still be substantially less than the costs associated with a single episode of surgical NEC. We will invite a parent to join the TSC and invite an additional independent member to the TSC from a charity or parent advocacy organisation. We will liaise with Tiny Lives charity and Bliss UK to consider the implications of our trial findings and disseminate the results.

Experience of research team members

We are an experienced research team, having recruited more than 1000 preterm infants to trials and studies in the last 10 years, including qualitative exploration of sensitive issue in parents whose babies did not survive. We are recognised internationally for our work on feeding and nutrition, and associated complications such as necrotising enterocolitis. We have worked closely with parents on all our studies (see above).

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Appendix 1: Breastfeeding Self-Efficacy Scale – Short Form

[24]Wheeler et al. 2013

Original Items

I can….

1. Determine that my baby is getting enough milk
2. Successfully cope with the breastfeeding situation (pumping and actual breastfeeding) like I have with other challenging tasks
3. Breastfeed my baby without using formula as a supplement
4. Ensure that my baby is properly latched on for the whole feeding
5. Manage the breastfeeding situation to my satisfaction
6. Manage to breastfeed even if my baby is crying
7. Keep wanting to breastfeed
8. Comfortably breastfeed with my family members present
9. Be satisfied with my breastfeeding experience
10. Deal with the fact that pumping and breastfeeding can be time consuming
11. Finish feeding my baby on one breast before switching to the other breast
12. Continue to breastfeed my baby for every feeding
13. Manage to keep up with my baby's breastfeeding demands
14. Tell when my baby is finished breastfeeding

Additional Items

1. Pump enough milk for my baby
2. Get help with breastfeeding if or when I need it
3. Determine when my baby needs to be fed
4. Switch from mostly pumping to mostly or completely breastfeeding my baby

Appendix 2: Edinburgh Postnatal Depression Scale (EPDS)

[26]Cox et al.

 I have been able to laugh and see the funny side of things.

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- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

I have looked forward with enjoyment to things.

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I have blamed myself unnecessarily when things went wrong.

- Yes, most of the time
- Yes, some of the time
- Not very often
- No, never

I have been anxious or worried for no good reason.

- No not at all
- Hardly ever
- Yes, sometimes
- Yes, very often

I have felt scared or panicky for no very good reason.

- Yes, quite a lot
- Yes, sometimes

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- No, not much
- No, not at all

Things have been getting on top of me.

- Yes, most of the time I haven't been able to cope at all
- Yes, sometimes I haven't been coping as well as usual
- No, most of the time I have coped quite well
- No, I have been coping as well as ever

I have been so unhappy that I have had difficulty sleeping.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

I have felt sad or miserable.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

I have been so unhappy that I have been crying.

- Yes, most of the time
- Yes, quite often
- Only occasionally
- No, never

☐ The thought of harming myself has occurred to me.

- ○ Yes, quite often
- ○ Sometimes
- ○ Hardly ever
- ○ Never

Appendix 3: data items

We will use standard definitions of disease and outcomes refined and validated in our previous studies to collect data including

- Standardized forms for: NEC/gut complications; sepsis; ROP grade and treatment at discharge; CLD at 36w; presence of IVH/PVL or PDA requiring treatment
- Day of first milk feed; receipt of buccal colostrum
- Time to full feeds sustained for 3 days; days of nil by mouth; age at first use of DHM, fortifier and formula milk
- Postnatal age at last breastmilk expression, first day of feeding from the breast, postnatal age at last received MOM, age at last breast feed (telephone report post-discharge)
- Maternal demographics: postcode/SES, age, parity, previous breastfeeding, previous breastfeeding for at least 3 months, smoking, major maternal disease e.g. diabetes etc.
- Validated questionnaire for breastfeeding self-efficacy (BSES)
- Validated questionnaire Edinburgh postnatal depression score (EPND)
- Costs associated with length of stay (days) for each category of care (intensive, high and low dependency) estimated using NHS HRGs
- Costs of DHM provided by Hearts Milk Bank includes transport, storage at site etc.

Appendix 4: Topic guide for interviews

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Parent Topic Guide for Interviews

Interviewer extends a special thanks to the mother for agreeing to take part in the research. Explain that the aims of the study are to seek the views and experiences about aspects of breastfeeding support and use of human donor milk. Reassure that it is OK for anyone else, including the father, to be present if the mother wishes. Make the point that she doesn't have to answer all questions.

Interviewer introduces herself and outlines the study

Explain use of the audio recorder – the interview is being audio recorded so I have an accurate account of what the participant has said and so that I don't have to take handwritten notes. Interviews will be anonymised when they are typed up prior to analysis (i.e. their names and any other information that could identify them are taken out.)

- Assure confidentiality.
- Ask whether they have any more questions about the study?
- Check they have signed the consent form and are happy
- Explain that the interview can be ended or postponed at any time.

Introduction

Can you tell me a little about how your baby is getting on at present?

Feelings and support before and after birth

- Did you think about breastfeeding before your baby was born?
- Have you breast fed before, or been to any antenatal classes on breastfeeding?
- Did having a premature baby change what you thought or felt?

Patient Information

- Did anyone speak to you about expressing breastmilk shortly after the birth?
- Do you think you were given enough information or support?
- Did you feel empowered to make an informed decision or did you feel pressurised?
- In what ways could the information or support you were given be improved?
    - explanations
    - information to read
    - other?

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Feelings and support whilst on the NICU

- Do you think the staff were sensitive to your opinions and any challenges you had?
- What could staff have done to improve support for you?
- Did you feel supported by friends, partners and other family members?
- Looking back, how do you feel your experience of providing breastmilk was for this baby?
- What do you think about the use of human donor milk or formula milk?
- Would you have preferred your baby to receive donor milk for longer?
- If money (NHS costs) was not an issue, do you think other babies should be offered donor milk if the mum is struggling to breast feed? E.g. a term baby where the mother is unwell, or has a poor milk supply?

End of interview

I have reached the end of my questions. Is there anything you would like to add?

How did you feel about the interview?

- Are there any questions you would like to ask me about the study?
- Thank them for giving up their time and supporting the study.
- Ask them if they still agree for the interview to be analysed.

Explain they can find a summary of the findings on the website www.neonatalresearch.net at the end of the study.

BMJ Paediatrics Open

A protocol for a pilot randomised controlled trial exploring human milk, nutrition, growth, and breastfeeding rates at discharge: The Hummingbird study

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Hummingbird study

A protocol for a pilot randomised controlled trial exploring human milk, nutrition, growth, and breastfeeding rates at discharge: The Hummingbird study

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ABSTRACT

Introduction

Mother's own breast milk (MOM) is the optimal nutrition for preterm infants as it reduces the incidence of key neonatal morbidities and improves long-term outcomes. However, MOM shortfall is common and either preterm formula or pasteurised donor human milk (DHM) may be used, although practice varies widely. Limited data suggest that the use of DHM may impact maternal beliefs and behaviours and therefore breastfeeding rates. The aim of this pilot study is to determine if a longer duration of DHM exposure increases breastfeeding rates, and if a randomised controlled trial (RCT) design is feasible.

Methods and analysis

The Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge (HUMMINGBIRD) study is a feasibility and pilot, non-blinded RCT with a contemporaneous qualitative evaluation. Babies born less than 33 weeks gestation or with birth weight <1500 grams whose mothers intend to provide MOM are randomly assigned to either control (DHM used to make up shortfall until full feeds and preterm formula thereafter) or intervention (DHM used for shortfall until 36 weeks corrected age or discharge if sooner). The primary outcome is breastfeeding at discharge. Secondary outcomes include growth, neonatal morbidities, length of stay, breastfeeding self-efficacy and postnatal depression using validated questionnaires. Qualitative interviews using a topic guide will explore perceptions around use of DHM and analysed using thematic analysis.

Ethics approval and dissemination

Nottingham 2 Research Ethics Committee granted approval (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. Results will be disseminated in peer-reviewed journals.

Trial registration: Trial was registered prospectively on 4th May 2021 (ISRCTN 57339063).

INTRODUCTION

Approximately 60,000 babies are born prematurely (<37 weeks) in the UK each year and around 10,000 babies are born very preterm (<32 weeks' gestation) (1). While survival rates of extremely preterm (<28 weeks) infants have improved recently, serious adverse outcomes including late onset sepsis (LOS) and necrotising enterocolitis (NEC) remain common (2, 3). Preterm infants are at significant risk of long-term complications including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and cognitive impairment (4). Nutritional management impacts short and long-term outcomes (5) but remains challenging as macronutrient intakes can be hard to meet (6).

Mother's own milk

Mother's own milk (MOM) provides the basis of the optimal diet for preterm babies due to its composition including key proteins and lipids, as well as enzymes, growth factors and other unique dyad-specific bioactive nutrients such as human milk oligosaccharides (HMOs) (7). Use of MOM is associated with a dose-response decreased risk of neonatal morbidities such as NEC, LOS, and BPD (8-11). Whilst an exclusive MOM diet has been associated with slower growth compared to preterm formula (PF) (12, 13), cognitive, cardiac, and metabolic outcomes are better (14-16).

Challenges of expressing MOM and breastfeeding in NICU

Despite well recognised benefits of MOM, low breastfeeding rates remain a major health concern. Over 90% of mothers delivering prematurely now provide some breastmilk, but breastfeeding rates at discharge vary considerably across the UK (25-91%)(17). Mothers of preterm babies must cope with the stress of having a preterm, sick infant and maintain

breastmilk expression for several weeks. Furthermore, the initiation of lactogenesis is often impaired after preterm birth (18), and despite targeted support, infants require additional milk at some stage (17).

Donor Human Milk

The World Health Organisation, American Association for Pediatrics and European Society of Paediatric Gastroenterology, Hepatology and Nutrition recommend the use of donor human milk (DHM) for feeding premature infants as a first alternative when there is a MOM shortfall (7, 19), despite few high-quality RCTs and heterogeneity of studies. A recent Cochrane review suggested that DHM may reduce the risk of NEC compared to preterm formula (PF), with at least 33 infants needing to receive DHM to prevent one NEC case. The data do not support a reduction in mortality or longer-term neurodevelopmental benefits (20). Differences in DHM use exist amongst UK NICUs (21), with some only providing DHM for the first 10 days whereas other units use DHM for closer until discharge. Variation between NICU maybe linked to uncertainties around DHM use including whether DHM affects duration of breastmilk expression or breastfeeding (22). A systematic review showed that DHM may have a positive effect on *any* breastfeeding but rates of *exclusive* breastfeeding on discharge are unchanged (23). A large observational study in 56 NICUs in the USA showed increased rates of breastfeeding in NICUs where a DHM programme was implemented, along with a decrease in NEC rate (24). In contrast, another single-centre retrospective study showed that MOM provision *decreased* following the implementation of a donor milk program and preterm infants consumed less MOM in the first 14 days in the post-DHM cohort (25). Esquerra-Zwiers showed similarly reduced MOM use in the first 14 days of life with DHM availability. However, in this study enteral feeds were commenced

earlier, and infants were exposed to formula later in life in after DHM introduction (26). More recently, DHM used in addition to optimising breastfeeding support and kangaroo care led to improved exclusive human milk feeding (27). To date, no RCT has studied the relationship between donor milk availability and breastfeeding at hospital discharge.

Preterm formula

The composition of PF is designed to meet the high-nutrient demands of the preterm infant and results in improved weight gain, linear and head growth (20). However, no RCTs have shown improved long-term growth or neurodevelopmental outcomes compared to use of MOM or DHM (20, 28). PF may provide a more consistent delivery of macro- and micro-nutrients but generally lacks bioactive component, which might be key in reducing disease and improving long-term outcomes (29, 30). The cost of PF (around £5 per litre) is almost 30-fold lower than the cost of DHM (between £125-150 per litre). However, systematic review of economic evaluations of DHM determine it is a cost-effective intervention because it reduced occurrence of NEC by two thirds compared to formula (31).

Summary of key issues: donor human milk as a 'complex intervention'

Whilst MOM is the optimal source of nutrition for preterm infants, rates of breastmilk feeding could be improved. Around 90-95% of mothers in the North East start breastmilk expression, but only 35% still provide breastmilk at discharge compared to the national average of 60% (32). Improving availability of MOM is crucial to reducing key neonatal morbidities. DHM use is increasing in most UK neonatal units and is recommended by ESPGHAN when there is a MOM shortfall (7). However, because DHM may affect growth, the optimal strategy for improving lifelong health remains uncertain. Observational data

show that DHM availability is associated with breastmilk expression and breastfeeding duration suggesting that DHM affects beliefs and behaviours of mothers and perhaps healthcare staff, and DHM is therefore a 'complex intervention'. Complex interventions in healthcare influence biology (i.e. health and disease) as well as behaviour and belief (e.g., breastfeeding rates). Complex interventions may have multiple relevant outcomes and mechanistic causal pathways; and may be affected by context e.g. NICUs with differing background rates of NEC or breastfeeding. Like many other complex interventions, there is a long lag time between dietary interventions such as DHM and outcomes, e.g. metabolism and cognition in adulthood (33).

Provision of DHM may be the best example of a complex intervention in neonatal medicine, and uncertainties around the optimal strategy are unlikely to be resolved with a single RCT. We designed this pilot trial to determine the foundation for further trials that can investigate the optimal implementation and use of DHM (Figure 1).

METHODS AND ANALYSIS

The HUMMINGBIRD study is a randomised open-label controlled trial in two tertiary neonatal units in the North East of England, the second site being added in May 2022. It is designed to compare two different nutritional strategies both of which use DHM to make up any shortfall in MOM for preterm infants, but provided until two points of time – full feeds vs 36 weeks corrected age (ca) (Table 1).

Setting	Tertiary level NICUs in North East England
Population	Preterm infants <33 weeks or with a birth weight <1500g admitted in the first seven days of life

Intervention	Use of DHM to make up any shortfall in MOM until 36 weeks corrected age (or discharge if this comes earlier)
Control	Use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours)
Design	Randomised open-label controlled trial
Timeframe	Until 36 weeks corrected gestation or hospital discharge if earlier

Table 1. Summary of study methods

Population

Infants born before 33 completed weeks of gestation or with a birth weight of less than 1500 g whose mothers intend to express breastmilk after delivery and are willing to accept DHM are eligible. Only infants with written informed consent from parents and randomised within seven days of birth can be included. Infants who were born with major congenital or life-threatening abnormalities or who were exposed to formula milk prior to randomisation are excluded.

Intervention: DHM to 36 weeks

DHM is used to make up any shortfall in MOM until 36 weeks ca. If infants do not experience any shortfall, they will continue to receive MOM. This study aims to assess the effect of DHM on breastfeeding at discharge, therefore infants in the intervention group will only continue to receive DHM if their mother is still expressing breastmilk. Where the infant has not received any MOM for one week, or where the mother has told clinical staff she stopped expressing, the use of DHM will be discontinued and the baby will receive PF.

Control: DHM until full feeds only

DHM is used to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours). If a shortfall of MOM occurs beyond this point, infants in the control group will receive PF.

Infants in both arms follow standard routine care. Human milk feeds (both MOM and DHM) are fortified with human milk fortifier once full feeds are achieved.

Randomisation

Infants are randomised with a secured, password protected web-based randomisation tool (www.sealedenvelope.com) using random permutated blocks and stratification incorporating the following strata: gestation (<28 weeks yes/no), and twin/triplet status (yes/no). Twins, triplets, and higher multiples are co-randomised to the same trial arm.

Data collection and management

Feeding data are collected prospectively on a daily basis by research team. Trained research team members perform measurements weekly on each infant at care times. Length is measured using Leicester Incubator Measure. Head, mid-arm, and thigh circumference are measured using single-use tape measure. Combined UK-WHO growth charts for preterm infants are used as a reference to calculate centiles and Z-scores. Trial completion is defined as reaching 36 weeks ca or earlier if infant is discharged home or to a postnatal ward. Data about neonatal morbidities are collected at this stage. Families are contacted via telephone

by research team members at around 6 and 12 weeks' time from discharge. Data about type of feeding, milk, recent weight, and head measurements are obtained. All data are recorded electronically, and confidential data are password secured.

Study Outcomes

Primary outcome

Any breastfeeding, or mother still actively expressing milk, at 36 weeks corrected age or discharge if this is earlier.

Secondary outcomes – growth, feeding and neonatal outcomes

1. Growth – weekly weight, length, head, mid-arm and thigh circumference, absolute changes (g/kg/day and mm/week) and change in standard deviation score.
2. Neonatal morbidities:
    a. Episodes of confirmed NEC Bell stage 2 or greater
    b. LOS confirmed and clinically suspected according to existing case definitions (34)
    c. Severe BPD (oxygen requirement or respiratory support at 36 weeks ca)
    d. ROP – worst stage and zone
    e. Intraventricular haemorrhage – worst grade recorded and/or cystic periventricular leukomalacia

3. Days of intensive, high, and low dependency care (35); ca at discharge, total length of stay (days)
4. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks ca
5. Age at starting breastmilk fortifier and number of days when fortifier is provided
6. Type of feeding at discharge (direct breast feeding, tube feeding etc.)
7. Type of milk and feeding, weight and head circumference at 6- and 12-weeks post discharge

Secondary outcomes – maternal questionnaires and qualitative data

A validated questionnaire, Breastfeeding Self-Efficacy Scale – Short Form (BSES-SF) adapted for preterm infants (36), is given to mothers at two time points – around 10 days postnatal age and again at 36 weeks ca or prior to discharge if sooner. The Edinburgh Postnatal Depression Scale (EPDS) questionnaire is also administered to mothers around day 10 postpartum (37). BSES-SF and EPDS scores will serve as a guide to ensure that mothers both spectrums (with scores in in the bottom and top quartile) will be represented in the subset chosen for interviews.

Qualitative interviews with mothers will be conducted to explore perceptions around DHM use and barriers and facilitators to expressing MOM. These one-to-one, in-person semi-structured interviews will be audio-recorded and transcribed. We estimate that 15-20 interviews will be recorded although final number of interviews will be determined by

thematic saturation generated through interpretation of data (38). Qualitative data will also inform whether an "RCT" design was problematic or unacceptable for mothers.

DHM is a complex intervention and its effect on breastfeeding has not been studied in RCTs. Therefore, feasibility of RCT design to answer this research question will also be assessed. Data on how many patients declined DHM, did not wish to enrol or were lost to follow up will be included. Protocol deviations frequency will be observed. This knowledge will provide data to design future definitive trials.

Hypothesis, sample size and power

We hypothesise that longer access to DHM (intervention) will improve the rate of breastfeeding at discharge from the local rate of 35% in our NICU to the UK average of 60%. Fifty-eight infants per trial group will be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive, at least 130 infants need to be recruited to complete the trial. We estimate that up to 20% of infants may be discharged before 36 weeks ca to other neonatal units that do not have access to DHM. We will therefore need to recruit between 130 and 156 infants for the study to be powered at 80%, and we estimate this will take 18-24 months recruitment.

Analysis

Data will be analysed using an intention-to-treat approach. Additional analysis will be performed using breastfeeding outcome data for those completing the study (i.e., excluding transfers) and the first baby from a multiple pregnancy enrolled. Categorical data will be presented as counts and frequencies and will be compared using chi squared or Fisher exact

test as appropriate. Morbidities will use logistic regression. Continuous data will be presented as mean (SD) or median (IQR) and the Shapiro-Wilk test will be used to test the normality of the data. Group differences in continuous data will be compared using Student's t-test or Mann-Whitney U test for normally and non-normally distributed data respectively or quantile regression as appropriate. Feeding data will be compared using multinomial statistics. All tests will be performed two tailed and $p<0.05$ will be deemed statistically significant. Qualitative data will be analysed using reflexive thematic analysis (39).

Patient and Public Involvement

The study involved discussion with parents and is aligned with the James Lind alliance priority setting that identified feeding and nutrition as key areas for research in preterm infants. A trial steering committee including parents oversees trial conduct and progress. The trial is compliant with the UNICEF Baby Friendly Initiative.

What is already known on this topic:

MOM benefits for preterm infants are well recognised but uncertainties remain around the optimal strategy for DHM use, especially whether it impacts ~~on~~ breastfeeding. DHM is a complex intervention which has effects on infant health and maternal and healthcare staff behaviours and beliefs.

What this study adds:

This pilot RCT strives to determine if DHM provision affects breastfeeding rate at discharge and if RCT is a suitable design to answer this research question.

How this study might affect research, practice or policy:

A single RCT of a complex intervention is unlikely to resolve all uncertainties. Studies incorporating quantitative and qualitative methods may better elucidate the role of DHM in NICUs. HUMMINGBIRD may help optimise the design of future studies in larger scale.

ETHICS APPROVAL AND DISSEMINATION

Nottingham 2 Research Ethics Committee granted approval for HUMMINGBIRD Study on 6th April 2021 (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. Results will be disseminated in peer-reviewed journals and discussed with Tiny Lives Charity and Bliss UK to consider the implications of findings.

COMPETING INTERESTS

NS is the cofounder of the Human Milk Foundation, a UK charity that provides donor human milk. NE and JB report research grants paid to their institution from National Institutes for Health Research, Action Medical Research, Prolacta Biosciences US, Danone Early Life Nutrition and NeoKare but received no personal fee, and have no other financial conflicts related to industry funding. NE reports lecture honoraria from Nestle Nutrition Institute donated to charity, and Astarte Medical.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors and was supported using internal departmental funds.

AUTHORS' CONTRIBUTIONS

NE had original idea for HUMMINGBIRD after discussions with NS and played a key role in developing the protocol. JB contributed to study design and protocol development. All authors contributed to the writing and review of this paper and gave final approval for its submission.

ACKNOWLEDGMENTS

Not applicable.

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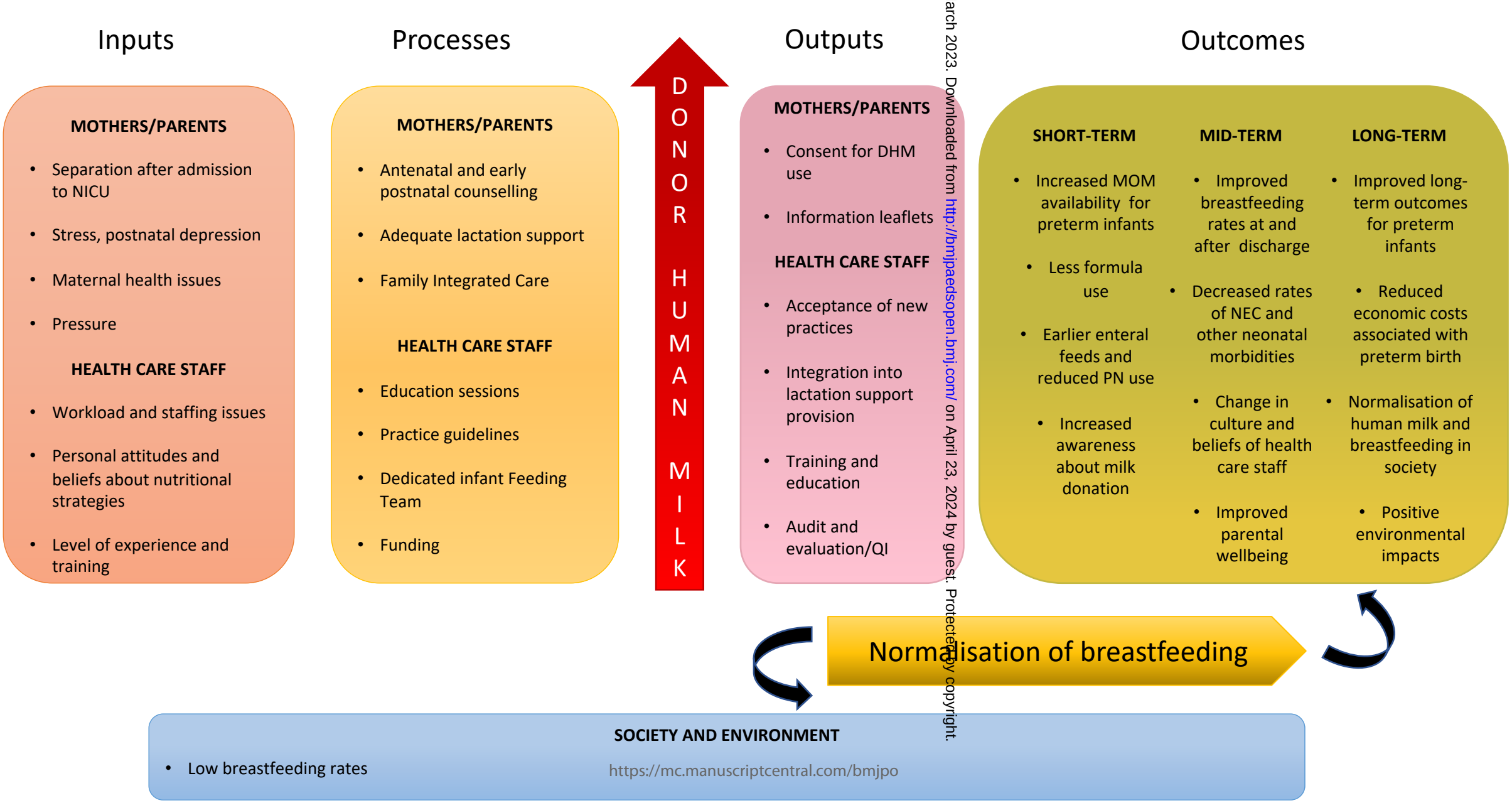

Human Mllk, Nutrition, Growth, and Breastfeeding Rates at Discharge: The Hummingbird Study

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Sponsor: Newcastle Hospitals NHS Foundation Trust

IRAS Project ID: 281071

Sponsor Protocol number: NuTH 09735

Trial registration number: ISRCTN

REC reference number:

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Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

Contents

Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

Trial Steering Committee (TSC)

Name	Role
TBC	Independent chair
Dr Nicholas Embleton	Chief Investigator
TBC	Parent
TBC	BFI/Advocacy rep
Maria Douglass	Breast feeding support nurse
Professor Judith Rankin	Co-investigator
Dr Janet Berrington	Co-investigator
Dr Stefan Zalewski	Co-investigator

Study proposal summary

This is the protocol proposal for a single site, non-blinded, randomised controlled trial exploring two currently used dietary regimes in preterm infants. The dietary regimes involve fully supporting mothers to provide their own expressed breast milk and using donor human milk to make up any shortfall in breastmilk supply. The primary outcome is maternal breastfeeding rates at discharge. Mothers of infants on ward 35 neonatal unit at the Royal Victoria Infirmary will be approached by clinical team members, and infants will be enrolled after signed informed consent. Infants do not undergo any additional interventions or tests, and all data used is routinely collected. Mothers will complete short questionnaires on two occasions and a subset invited to take part in qualitative interviews. The study intervention finishes at hospital discharge, but two telephone calls post-discharge will be made to ascertain duration of any prolonged breastfeeding

Title (Acronym)	Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge: **The Hummingbird Study**
Study centre	Ward 35, Newcastle Royal Victoria Infirmary. Additional sites may be added

Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

Study objectives	To compare two dietary regimes that both use mother's own breastmilk and donor human milk to make up any volume shortfall
Study design	Randomised open label, controlled trial
Study population	Inclusion criteria • Preterm infants born <33 completed weeks of gestation or <1500g birthweight • Admitted to neonatal unit in first week of life • Written informed consent from parents • Maternal intention to provide breastmilk after birth Exclusion criteria • Parents unwilling to accept donor human milk • Major congenital or life-threatening abnormalities • Inability to randomise within 7 days of birth • Exposure to formula milk product prior to randomisation
Interventions	Donor human milk until full milk feeds established (control) compared to donor human milk until discharge for as long as the mother is still providing her own milk
Target number of patients	130-160 infants
Randomisation	Minimisation incorporating the following variables: gestation (<28 weeks yes/no), and twin/triplet status (yes/no) Secured, password protected web-based randomisation using minimisation algorithm (www.sealedenvelope.com or similar)
Primary outcomes	Breastfeeding at hospital discharge or 36 weeks corrected age
Secondary outcomes	Feed and growth-related outcomes Neonatal morbidities and clinical outcomes Maternal breast-feeding self-efficacy & postnatal depression scores Thematic analysis of qualitative interviews (subset)
Duration of trial intervention	36 weeks postmenstrual age or hospital discharge (which ever earlier)
Duration of study	Recruitment period: 18 months Total trial duration: 21 months

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End of Trial	Discharge from neonatal unit at Newcastle
Safety assessments	Routine assessments until discharge from Ward 35 Neonatal Unit Safety tracking during hospitalisation

Introduction

Around 10% of all births are premature, but whilst the majority do not require specialist medical treatment, those born very preterm (<32 weeks gestation) require prolonged hospital stay including intensive care. Survival in these infants has increased dramatically in recent years, but death is still common (~10% overall) as are the consequences of life-long physical and cognitive impairment.[1] In the UK around 10,000 premature infants are born every year, representing an annual cost to the NHS of ~£3 billion.[2]

The commonest cause of death or serious illness in preterm infants after the first few days are gut complications such as necrotising enterocolitis (NEC) or septicaemia.[3] Morbidity and mortality is lower in infants who receive mother's own expressed breastmilk (MOM) but >80% still require additional milk supplementation.[4] This is because there is often a 'shortfall' in maternal milk supply either due to inadequate lactation, or because mothers choose to discontinue expressing breastmilk before infants' are discharged home. Over 90% of mother's now provide at least some breastmilk, but breastfeeding rates at discharge vary considerably from 30-80% depending on hospital.[5] Low rates of breastfeeding are a major health concern, as there is strong evidence that breastfeeding throughout infancy is beneficial for cognitive and metabolic outcomes (e.g. obesity, high blood pressure etc.) in childhood and throughout the life-course.[6,7]

Use of donor human milk (DHM)

When there is a shortfall in MOM supply, an alternative milk is needed, which is either formula milk, or pasteurised, donated, human milk (DHM).[6,8] DHM is provided from one of ~12 donor milk banks in the UK which collect milk from UK donors. DHM must be tested, pasteurised, frozen and transported to hospitals for use. Because of this DHM is much more expensive (£150/litre) than formula milk (£5/litre). Studies also suggest that DHM may be less beneficial than mother's own milk at reducing neonatal disease, and strong support for mothers to provide their own milk is universally accepted.[9]

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DHM has been widely used for >30 years in the NHS, but there is no national system for supply, and use varies dramatically: some clinical networks do not use it at all, whereas others provide it routinely to all preterm infants.[10] No trial has ever been powered to determine a realistic reduction on rates of necrotising enterocolitis (NEC) or sepsis and such a trial would probably need to recruit at least 2500 infants.[4] There have been no large UK trials of donor human milk in preterm infants ever, and no nationally agreed, evidenced based guidelines for use exist.[10] The only two, recent, moderately sized (300-400 infants) RCTs showed differing effects. A Canadian trial showed no improvement on the primary outcome of cognitive outcome in infancy, although NEC was lower in a secondary analysis; however, there was no impact on survival.[11,12] A larger Dutch trial showed no effect on death, NEC or sepsis (combined primary outcome) although DHM was only provided for the first 10 days of life.[13] Our current Cochrane meta-analysis concluded that there is no evidence for a reduction in death, or any long-term benefits, but whilst NEC may be lower around 33 infants would need to receive DHM to prevent one case.[4]

In the last 20 years we identified only 5 RCTs including just 1200 infants in total, of which only one study was conducted in Europe. No trials included a qualitative analysis and economic analyses was only conducted in one trial which showed no difference in costs to 18 months age. In the UK, the healthcare costs of DHM need to be considered in order to determine which infants should receive DHM. Inconsistent observational data suggest an impact of donor milk on breast feeding rates, but no trials reported the impact on continued breastfeeding at discharge.[14] Our systematic review concluded that whilst there may be an impact on breastfeeding at discharge where DHM is used (perhaps by creating a more positive culture of breastfeeding), the effect was weak and inconsistent.[15]

Whilst all neonatal units now strive to support mothers to provide breastmilk, proponents of DHM argue that it's use creates a more positive effect on mother's, as well as health professional belief and culture, will result in longer duration of breastmilk expression, and ultimately duration of breast-feeding. However, whilst there are observational data, this has never been tested in well-designed RCTs, and a recent systematic review determined the overall impact was equivocal.[15] Nevertheless, increasing numbers of women, and support groups, now advocate for universal use of DHM in vulnerable infants throughout hospital stay, despite the lack of conclusive data and high-quality health economic evaluation.[16–18]

Current practice of DHM in the UK

Despite the widespread use of DHM, indications and practical use varies widely between Neonatal Intensive Care Units (NICUs) and hospitals. Some NICUs restrict use to only those infants born <28 weeks whereas others provide to all infants <32-34 weeks or <1500g. Some hospitals also use DHM for term born infants with cardiac and gut conditions, and in some situations, parents have asked for DHM to be used in term born infants where maternal supply is inadequate. In the first few days when milk feeds are established in preterm infants only relatively small DHM volumes are required, but volume (and therefore costs) increase as the infant grows. Clinical practice in NICUs in the UK varies widely.[10,19,20] Some NICUs only use DHM until full milk feeds have been established. This is because most key events linked to feeding (sepsis, NEC and other severe illness) occur in the first 10 days. However, other units will use DHM until closer to discharge because some clinicians feel this is more likely to support longer term breast feeding.

A further challenge arises because human breast milk alone will not meet the nutrient requirements for preterm infants.[21] To meet the higher nutrient requirements of preterm infants, commercially produced breast-milk-fortifiers (BMF) are added to mothers' own milk or donor milk. Although human milk-based fortifiers are available these are not widely used outside the USA and are very expensive.[22] BMF is therefore produced from cow's milk and is therefore a similar product to cow's milk infant formula. Many clinicians feel that rather than adding BMF to donor milk it would be preferable to use a milk formula.[20] This is because growth is slower in infants receiving DHM, and there are concerns that slow early growth may increase the risk of other problems, including worse cognitive outcomes. In addition, the continued use of DHM after full feeds are established in a typical preterm infant at 28 weeks born weighing 1000g, would cost around £1000-2000 more where the infant receives all DHM compared to infants receiving formula (in the situation where mothers do not provide any breastmilk).

Summary of key issues

In summary, use of donor human milk is commonplace in most UK neonatal units and despite the lack of a conclusive evidence base seems likely to remain a common choice for many clinicians where there is a shortfall in mothers' own milk. Most parents appear to favour use of DHM, and DHM is also strongly supported by advocacy groups including the WHO and UNICEF. There is no consistent approach to the use of DHM once feeds are established, and growth is faster when formula is used. DHM is also more expensive compared to formula. DHM may improve breastfeeding rates at discharge, and/or improve maternal self-efficacy for breast feeding, but if there are no additional

benefits from more prolonged use then resources may be better spent elsewhere, for example by employing more lactation specialists to support mothers to provide their own milk.

Proposed study to explore impacts on breastfeeding

The Hummingbird study is designed to compare two clinical dietary approaches, both of which are routinely used in the UK, by comparing the use of DHM to make up any shortfall in MOM until full feeds (control) to that of using DHM for a longer duration up to the pre-discharge period (intervention).

- **Setting**: Tertiary level NICU on ward 35, Royal Victoria
- **Population**: preterm infants <33 weeks or <1500g admitted in the first 7 days of life
- **Intervention**: use of DHM to make up any shortfall in MOM until 35-36 weeks corrected age (or the initiation of breast feeding)
- **Control**: use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours) and use of preterm formula milk to make up shortfall thereafter
- **Primary outcome**: any breastfeeding at 36 weeks corrected age or hospital discharge if this is earlier. This outcome is also met if a mother is still actively expressing breastmilk which the infant receives wholly or in part via a bottle/
- **Study design**: non-blinded randomised controlled trial
- **Timeframe**: until 36 weeks corrected gestation or hospital discharge is earlier

Currently around 90-95% of our mother's start expression of breastmilk for their baby, but only 35% are still providing breastmilk at discharge compared to the national average of 60%.[5,23] The rate in the North East of England is around the lowest in the UK. Mothers who choose or are unable to continue providing MOM may do this at any point in time after they have started. Because this study is designed to impact on breastfeeding at discharge, infants in the intervention group will only continue to receive DHM if their mother is still continuing to provide breastmilk. Where the infant has not received any mother's own breastmilk for 1 week, or where the mother has told clinical staff she is no longer expressing, we will discontinue use of DHM, and the baby will receive a standard formula milk designed for preterm infants.

Secondary outcomes – growth and neonatal outcomes

We will collect a range of relevant common neonatal secondary outcomes:

1. Growth – weekly weight, length and head circumference, mid-arm/thigh where feasible, absolute changes (g/kg/day and mm/week) and change in standard deviation score

2. Episodes of NEC, sepsis - confirmed and clinically suspected according to existing nationally agreed case definitions
3. Chronic lung disease, Retinopathy of prematurity (ROP), Intraventricular haemorrhage, Cystic PVL etc.
4. Days of intensive, high and low dependency care; age at discharge, total length of stay
5. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks
6. Age at starting fortifier
7. Type of feeding at discharge (direct breast feeding, tube feeding etc.)

Secondary outcomes – breastfeeding self-efficacy and thematic analysis of interviews

We will use a mixed methods approach to determine maternal breastfeeding self-efficacy expression and conduct qualitative interviews in a subset of up to 20 mothers. We will use two short validated questionnaires – the Breast-feeding Self-efficacy Scale – Short form (BSES-SF)[24,25] and the Edinburgh Postnatal Depression Scale[26] - at two time points: between 5-10 days of age and again at 35-36wca or prior to discharge if sooner. These only take around 1-2 minutes to complete. We will use the BSES-SF scores to identify women in the top and bottom quartiles of scores and invite up to 10 women per trial group to take part in a qualitative tape-recorded interview. This will be transcribed and analysed using thematic analysis. We will develop a topic guide based on the questions on the BSE-SF and our experience (see appendix). Interviews will be conducted by a single member of the research team (KC) shortly before or after hospital discharge. We will seek consent to keep in touch with parents after discharge. We will also ask for consent to keep in telephone contact with mothers who are breastfeeding at discharge at 1-2 monthly intervals in order to simply ascertain duration of breastfeeding.

Sample size and Power

We hypothesise that prolonged use of DHM will improve the rate of breastfeeding at discharge from 35% to the UK national average of 60%. Fifty-eight infants per trial group would be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive we will need to recruit at least 130 infants who are still receiving care at the RVI at ~36 weeks corrected age (wca). We estimate that up to 20% of infants may be discharged before 36wca to a local hospital that does not have continued access to DHM. We will therefore need to recruit between 130 and 156 infants in order that we are powered to determine the primary outcome. The NICU on ward 35 admits ~160 babies every year <1500g or <33 weeks of whom we expected around 80% of infants will be enrolled (based on previous RCTs we conducted). Therefore, we estimate we will need a 12-18 months recruitment period so we can enrol at least 130 infants who achieve the primary outcome. Twins and triplets will be co-randomised to the same trial arm. We will analyse the data for all infants

using an intention-to-treat approach, but we will perform additional analysis only using breastfeeding outcome data for the first twin enrolled.

Funding

This trial will use dietary treatments already used in this way on the neonatal unit and collect routinely available electronic clinical data extracted from e-record and Badger neonatal database and inputted into an excel worksheet. There are no costs for use of questionnaires. Trial recruitment, consenting and interviews will be conducted by a member of clinical staff who has time available as part of daily activities (KC) supported by the neonatal research nurse. Costs for ISRCTN registration, printing, paperwork, tape recording, transcription, and travel costs for membership of the TSC will be met out of existing departmental research funds.

Trial registration, Ethics, HRA and risk burden

The trial will be registered on ISRCTN prior to opening. We will apply for HRA and REC approvals and apply for adoption onto the NIHR portfolio. There are no specific ethical issues with this trial, but we recognise the additional burden placed on parents by being asked to consider trial enrolment. There are no additional safety issues as part of the trial per se Use of donor breastmilk could be associated with theoretical risks (although none have been documented) or inadvertent use of the 'wrong' milk, but donor milk is already used in routine practice and this trial does not increase the risk. No additional interventions or tests are applied to infants as part of the trial. The questionnaires do ask sensitive information but only members of the clinical team will see the responses and will already be aware of important family and mental health issues as part of routine family centred care on the neonatal unit. Where the mother wishes, we will use the questionnaire responses to provide further targeted support to help her. The trial is fully compliant with national recommendations and Baby Friendly Initiative (BFI) part of UNICEF.

Patient Public Involvement and importance to the NHS

We have discussed this study with parents on the neonatal unit, and other parents after discharge. Parents tell us that the risks and complication associated with feeding preterm infants, and the stress of being able to provide breastmilk for their infant are very important issues. In addition, the James Lind alliance (JLA) priority setting www.jla.nihr.ac.uk/priority-setting-partnerships/preterm-birth/top-10-priorities/ identifies feeding and nutrition as very important. Our study focuses on key JLA priorities (i) what is the optimum milk feeding strategy (ii) what type of support is most effective in improving breastfeeding and will provide additional information relevant for a further 2 additional priorities (iii) how can infection be better prevented (iv) what interventions are most effective at preventing NEC. This trial is of major relevance to the NHS and studies interventions and outcomes highlighted in a recent top research priority setting in preterm infants.[27] Breastfeeding is a major national priority and

is an intervention that has potential to benefit marginalised and poorly resourced groups. Breastfeeding support in the community is essential to continued successful breastfeeding but is recognised as being inadequate in many settings. NEC is a devastating condition, and half of the infants requiring surgery die or have long-term serious disability. Donor human milk is an important cost for the NHS, but the total costs of DHM even for a large NICU will still be substantially less than the costs associated with a single episode of surgical NEC. We will invite a parent to join the TSC and invite an additional independent member to the TSC from a charity or parent advocacy organisation. We will liaise with Tiny Lives charity and Bliss UK to consider the implications of our trial findings and disseminate the results.

Experience of research team members

We are an experienced research team, having recruited more than 1000 preterm infants to trials and studies in the last 10 years, including qualitative exploration of sensitive issue in parents whose babies did not survive. We are recognised internationally for our work on feeding and nutrition, and associated complications such as necrotising enterocolitis. We have worked closely with parents on all our studies (see above).

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Appendix 1: Breastfeeding Self-Efficacy Scale – Short Form

[24]Wheeler et al. 2013

Original Items

I can….

1. Determine that my baby is getting enough milk
2. Successfully cope with the breastfeeding situation (pumping and actual breastfeeding) like I have with other challenging tasks
3. Breastfeed my baby without using formula as a supplement
4. Ensure that my baby is properly latched on for the whole feeding
5. Manage the breastfeeding situation to my satisfaction
6. Manage to breastfeed even if my baby is crying
7. Keep wanting to breastfeed
8. Comfortably breastfeed with my family members present
9. Be satisfied with my breastfeeding experience
10. Deal with the fact that pumping and breastfeeding can be time consuming
11. Finish feeding my baby on one breast before switching to the other breast
12. Continue to breastfeed my baby for every feeding
13. Manage to keep up with my baby's breastfeeding demands
14. Tell when my baby is finished breastfeeding

Additional Items

1. Pump enough milk for my baby
2. Get help with breastfeeding if or when I need it
3. Determine when my baby needs to be fed
4. Switch from mostly pumping to mostly or completely breastfeeding my baby

Appendix 2: Edinburgh Postnatal Depression Scale (EPDS)

[26]Cox et al.

 I have been able to laugh and see the funny side of things.

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- ◉ As much as I always could
- ○ Not quite so much now
- ○ Definitely not so much now
- ○ Not at all

I have looked forward with enjoyment to things.

- ○ As much as I ever did
- ○ Rather less than I used to
- ○ Definitely less than I used to
- ○ Hardly at all

I have blamed myself unnecessarily when things went wrong.

- ○ Yes, most of the time
- ○ Yes, some of the time
- ○ Not very often
- ○ No, never

I have been anxious or worried for no good reason.

- ○ No not at all
- ○ Hardly ever
- ○ Yes, sometimes
- ○ Yes, very often

I have felt scared or panicky for no very good reason.

- ○ Yes, quite a lot

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- Yes, sometimes
- No, not much
- No, not at all

 Things have been getting on top of me.

- Yes, most of the time I haven't been able to cope at all
- Yes, sometimes I haven't been coping as well as usual
- No, most of the time I have coped quite well
- No, I have been coping as well as ever

 I have been so unhappy that I have had difficulty sleeping.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

 I have felt sad or miserable.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

 I have been so unhappy that I have been crying.

- Yes, most of the time
- Yes, quite often

- Only occasionally
- No, never

The thought of harming myself has occurred to me.

- Yes, quite often
- Sometimes
- Hardly ever
- Never

Appendix 3: data items

We will use standard definitions of disease and outcomes refined and validated in our previous studies to collect data including

- Standardized forms for: NEC/gut complications; sepsis; ROP grade and treatment at discharge; CLD at 36w; presence of IVH/PVL or PDA requiring treatment
- Day of first milk feed; receipt of buccal colostrum
- Time to full feeds sustained for 3 days; days of nil by mouth; age at first use of DHM, fortifier and formula milk
- Postnatal age at last breastmilk expression, first day of feeding from the breast, postnatal age at last received MOM, age at last breast feed (telephone report post-discharge)
- Maternal demographics: postcode/SES, age, parity, previous breastfeeding, previous breastfeeding for at least 3 months, smoking, major maternal disease e.g. diabetes etc.
- Validated questionnaire for breastfeeding self-efficacy (BSES)
- Validated questionnaire Edinburgh postnatal depression score (EPND)
- Costs associated with length of stay (days) for each category of care (intensive, high and low dependency) estimated using NHS HRGs
- Costs of DHM provided by Hearts Milk Bank includes transport, storage at site etc.

Appendix 4: Topic guide for interviews

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Parent Topic Guide for Interviews

Interviewer extends a special thanks to the mother for agreeing to take part in the research. Explain that the aims of the study are to seek the views and experiences about aspects of breastfeeding support and use of human donor milk. Reassure that it is OK for anyone else, including the father, to be present if the mother wishes. Make the point that she doesn't have to answer all questions.

Interviewer introduces herself and outlines the study

Explain use of the audio recorder – the interview is being audio recorded so I have an accurate account of what the participant has said and so that I don't have to take handwritten notes. Interviews will be anonymised when they are typed up prior to analysis (i.e. their names and any other information that could identify them are taken out.)

- Assure confidentiality.
- Ask whether they have any more questions about the study?
- Check they have signed the consent form and are happy
- Explain that the interview can be ended or postponed at any time.

Introduction

Can you tell me a little about how your baby is getting on at present?

Feelings and support before and after birth

- Did you think about breastfeeding before your baby was born?
- Have you breast fed before, or been to any antenatal classes on breastfeeding?
- Did having a premature baby change what you thought or felt?

Patient Information

- Did anyone speak to you about expressing breastmilk shortly after the birth?
- Do you think you were given enough information or support?
- Did you feel empowered to make an informed decision or did you feel pressurised?
- In what ways could the information or support you were given be improved?
    - explanations
    - information to read
    - other?

Feelings and support whilst on the NICU

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- Do you think the staff were sensitive to your opinions and any challenges you had?
- What could staff have done to improve support for you?
- Did you feel supported by friends, partners and other family members?
- Looking back, how do you feel your experience of providing breastmilk was for this baby?
- What do you think about the use of human donor milk or formula milk?
- Would you have preferred your baby to receive donor milk for longer?
- If money (NHS costs) was not an issue, do you think other babies should be offered donor milk if the mum is struggling to breast feed? E.g. a term baby where the mother is unwell, or has a poor milk supply?

End of interview

I have reached the end of my questions. Is there anything you would like to add?

How did you feel about the interview?

- Are there any questions you would like to ask me about the study?
- Thank them for giving up their time and supporting the study.
- Ask them if they still agree for the interview to be analysed.

Explain they can find a summary of the findings on the website www.neonatalresearch.net at the end of the study.

BMJ Paediatrics Open

A protocol for a pilot randomised controlled trial exploring human milk, nutrition, growth, and breastfeeding rates at discharge: The Hummingbird study

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Hummingbird study

A protocol for a pilot randomised controlled trial exploring human milk, nutrition, growth, and breastfeeding rates at discharge: The Hummingbird study

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ABSTRACT

Introduction

Mother's own breast milk (MOM) is the optimal nutrition for preterm infants as it reduces the incidence of key neonatal morbidities and improves long-term outcomes. However, MOM shortfall is common and either preterm formula or pasteurised donor human milk (DHM) may be used, although practice varies widely. Limited data suggest that the use of DHM may impact maternal beliefs and behaviours and therefore breastfeeding rates. The aim of this pilot study is to determine if a longer duration of DHM exposure increases breastfeeding rates, and if a randomised controlled trial (RCT) design is feasible.

Methods and analysis

The Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge (HUMMINGBIRD) study is a feasibility and pilot, non-blinded RCT with a contemporaneous qualitative evaluation. Babies born less than 33 weeks gestation or with birth weight <1500 grams whose mothers intend to provide MOM are randomly assigned to either control (DHM used to make up shortfall until full feeds and preterm formula thereafter) or intervention (DHM used for shortfall until 36 weeks corrected age or discharge if sooner). The primary outcome is breastfeeding at discharge. Secondary outcomes include growth, neonatal morbidities, length of stay, breastfeeding self-efficacy and postnatal depression using validated questionnaires. Qualitative interviews using a topic guide will explore perceptions around use of DHM and analysed using thematic analysis.

Ethics approval and dissemination

Nottingham 2 Research Ethics Committee granted approval (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. Results will be disseminated in peer-reviewed journals.

Trial registration: Trial was registered prospectively on 4th May 2021 (ISRCTN 57339063).

INTRODUCTION

Approximately 60,000 babies are born prematurely (<37 weeks) in the UK each year and around 10,000 babies are born very preterm (<32 weeks' gestation) (1). While survival rates of extremely preterm (<28 weeks) infants have improved recently, serious adverse outcomes including late onset sepsis (LOS) and necrotising enterocolitis (NEC) remain common (2, 3). Preterm infants are at significant risk of long-term complications including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and cognitive impairment (4). Nutritional management impacts short and long-term outcomes (5) but remains challenging as macronutrient intakes can be hard to meet (6).

Mother's own milk

Mother's own milk (MOM) provides the basis of the optimal diet for preterm babies due to its composition including key proteins and lipids, as well as enzymes, growth factors and other unique dyad-specific bioactive nutrients such as human milk oligosaccharides (HMOs) (7). Use of MOM is associated with a dose-response decreased risk of neonatal morbidities such as NEC, LOS, and BPD (8-11). Whilst an exclusive MOM diet has been associated with slower growth compared to preterm formula (PF) (12, 13), cognitive, cardiac, and metabolic outcomes are better (14-16).

Challenges of expressing MOM and breastfeeding in NICU

Despite well recognised benefits of MOM, low breastfeeding rates remain a major health concern. Over 90% of mothers delivering prematurely now provide some breastmilk, but breastfeeding rates at discharge vary considerably across the UK (25-91%)(17). Mothers of preterm babies must cope with the stress of having a preterm, sick infant and maintain

breastmilk expression for several weeks. Furthermore, the initiation of lactogenesis is often impaired after preterm birth (18), and despite targeted support, infants require additional milk at some stage (17).

Donor Human Milk

The World Health Organisation, American Association for Pediatrics and European Society of Paediatric Gastroenterology, Hepatology and Nutrition recommend the use of donor human milk (DHM) for feeding premature infants as a first alternative when there is a MOM shortfall (7, 19), despite few high-quality RCTs and heterogeneity of studies. A recent Cochrane review suggested that DHM may reduce the risk of NEC compared to preterm formula (PF), with at least 33 infants needing to receive DHM to prevent one NEC case. The data do not support a reduction in mortality or longer-term neurodevelopmental benefits (20). Differences in DHM use exist amongst UK NICUs (21), with some only providing DHM for the first 10 days whereas other units use DHM for closer until discharge. Variation between NICU maybe linked to uncertainties around DHM use including whether DHM affects duration of breastmilk expression or breastfeeding (22). A systematic review showed that DHM may have a positive effect on *any* breastfeeding but rates of *exclusive* breastfeeding on discharge are unchanged (23). A large observational study in 56 NICUs in the USA showed increased rates of breastfeeding in NICUs where a DHM programme was implemented, along with a decrease in NEC rate (24). In contrast, another single-centre retrospective study showed that MOM provision *decreased* following the implementation of a donor milk program and preterm infants consumed less MOM in the first 14 days in the post-DHM cohort (25). Esquerra-Zwiers showed similarly reduced MOM use in the first 14 days of life with DHM availability. However, in this study enteral feeds were commenced

earlier, and infants were exposed to formula later in life in after DHM introduction (26). More recently, DHM used in addition to optimising breastfeeding support and kangaroo care led to improved exclusive human milk feeding (27). To date, no RCT has studied the relationship between donor milk availability and breastfeeding at hospital discharge.

Preterm formula

The composition of PF is designed to meet the high-nutrient demands of the preterm infant and results in improved weight gain, linear and head growth (20). However, no RCTs have shown improved long-term growth or neurodevelopmental outcomes compared to use of MOM or DHM (20, 28). PF may provide a more consistent delivery of macro- and micro-nutrients but generally lacks bioactive component, which might be key in reducing disease and improving long-term outcomes (29, 30). The cost of PF (around £5 per litre) is almost 30-fold lower than the cost of DHM (between £125-150 per litre). However, systematic review of economic evaluations of DHM determine it is a cost-effective intervention because it reduced occurrence of NEC by two thirds compared to formula (31).

Summary of key issues: donor human milk as a 'complex intervention'

Whilst MOM is the optimal source of nutrition for preterm infants, rates of breastmilk feeding could be improved. Around 90-95% of mothers in the North East start breastmilk expression, but only 35% still provide breastmilk at discharge compared to the national average of 60% (32). Improving availability of MOM is crucial to reducing key neonatal morbidities. DHM use is increasing in most UK neonatal units and is recommended by ESPGHAN when there is a MOM shortfall (7). However, because DHM may affect growth, the optimal strategy for improving lifelong health remains uncertain. Observational data

show that DHM availability is associated with breastmilk expression and breastfeeding duration suggesting that DHM affects beliefs and behaviours of mothers and perhaps healthcare staff, and DHM is therefore a 'complex intervention'. Complex interventions in healthcare influence biology (i.e. health and disease) as well as behaviour and belief (e.g., breastfeeding rates). Complex interventions may have multiple relevant outcomes and mechanistic causal pathways; and may be affected by context e.g. NICUs with differing background rates of NEC or breastfeeding. Like many other complex interventions, there is a long lag time between dietary interventions such as DHM and outcomes, e.g. metabolism and cognition in adulthood (33).

Provision of DHM may be the best example of a complex intervention in neonatal medicine, and uncertainties around the optimal strategy are unlikely to be resolved with a single RCT. We designed this pilot trial to determine the foundation for further trials that can investigate the optimal implementation and use of DHM (Figure 1).

METHODS AND ANALYSIS

The HUMMINGBIRD study is a randomised open-label controlled trial in two tertiary neonatal units in the North East of England, the second site being added in May 2022. It is designed to compare two different nutritional strategies both of which use DHM to make up any shortfall in MOM for preterm infants, but provided until two points of time – full feeds vs 36 weeks corrected age (ca) (Table 1).

Setting	Tertiary level NICUs in North East England
Population	Preterm infants <33 weeks or with a birth weight <1500g admitted in the first seven days of life

Intervention	Use of DHM to make up any shortfall in MOM until 36 weeks corrected age (or discharge if this comes earlier)
Control	Use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours)
Design	Pilot randomised open-label controlled trial
Timeframe	Until 36 weeks corrected gestation or hospital discharge if earlier

Table 1. Summary of study methods

Population

Infants born before 33 completed weeks of gestation or with a birth weight of less than 1500 g whose mothers intend to express breastmilk after delivery and are willing to accept DHM are eligible. Only infants with written informed consent from parents and randomised within seven days of birth can be included. Infants who were born with major congenital or life-threatening abnormalities or who were exposed to formula milk prior to randomisation are excluded.

Intervention: DHM to 36 weeks

DHM is used to make up any shortfall in MOM until 36 weeks ca. If infants do not experience any shortfall, they will continue to receive MOM. This study aims to assess the effect of DHM on breastfeeding at discharge, therefore infants in the intervention group will only continue to receive DHM if their mother is still expressing breastmilk. Where the infant has not received any MOM for one week, or where the mother has told clinical staff she stopped expressing, the use of DHM will be discontinued and the baby will receive PF.

Control: DHM until full feeds only

DHM is used to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours). If a shortfall of MOM occurs beyond this point, infants in the control group will receive PF.

Infants in both arms follow standard routine care. Human milk feeds (both MOM and DHM) are fortified with human milk fortifier once full feeds are achieved.

Randomisation

Infants are randomised with a secured, password protected web-based randomisation tool (www.sealedenvelope.com) using random permutated blocks and stratification incorporating the following strata: gestation (<28 weeks yes/no), and twin/triplet status (yes/no). Twins, triplets, and higher multiples are co-randomised to the same trial arm.

Data collection and management

Feeding data are collected prospectively on a daily basis by research team. Trained research team members perform measurements weekly on each infant at care times. Length is measured using Leicester Incubator Measure. Head, mid-arm, and thigh circumference are measured using single-use tape measure. Combined UK-WHO growth charts for preterm infants are used as a reference to calculate centiles and Z-scores. Trial completion is defined as reaching 36 weeks ca or earlier if infant is discharged home or to a postnatal ward. Data about neonatal morbidities are collected at this stage. Families are contacted via telephone

by research team members at around 6 and 12 weeks' time from discharge. Data about type of feeding, milk, recent weight, and head measurements are obtained. All data are recorded electronically, and confidential data are password secured.

Study Outcomes

Primary outcome

Any breastfeeding, or mother still actively expressing milk, at 36 weeks corrected age or discharge if this is earlier.

Secondary outcomes – growth, feeding and neonatal outcomes

1. Growth – weekly weight, length, head, mid-arm and thigh circumference, absolute changes (g/kg/day and mm/week) and change in standard deviation score.
2. Neonatal morbidities:
    a. Episodes of confirmed NEC Bell stage 2 or greater
    b. LOS confirmed and clinically suspected according to existing case definitions (34)
    c. Severe BPD (oxygen requirement or respiratory support at 36 weeks ca)
    d. ROP – worst stage and zone
    e. Intraventricular haemorrhage – worst grade recorded and/or cystic periventricular leukomalacia

3. Days of intensive, high, and low dependency care (35); ca at discharge, total length of stay (days)
4. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks ca
5. Age at starting breastmilk fortifier and number of days when fortifier is provided
6. Type of feeding at discharge (direct breast feeding, tube feeding etc.)
7. Type of milk and feeding, weight and head circumference at 6- and 12-weeks post discharge

Secondary outcomes – feasibility data

DHM is a complex intervention and its effect on breastfeeding has not been studied in RCTs. Therefore, the following feasibility elements will be assessed.

1. Number of patients who declined DHM
2. Number of patients who did not wish to enrol
3. Number of patients unable to continue the intervention
4. Number of patients who were lost to follow up
5. Protocol deviations frequency

Secondary outcomes – maternal questionnaires and qualitative data

A validated questionnaire, Breastfeeding Self-Efficacy Scale – Short Form (BSES-SF) adapted for preterm infants (36), is given to mothers at two time points – around 10 days postnatal age and again at 36 weeks ca or prior to discharge if sooner. The Edinburgh Postnatal Depression Scale (EPDS) questionnaire is also administered to mothers around day 10 postpartum (37). BSES-SF and EPDS scores will serve as a guide to ensure that mothers both spectrums (with scores in in the bottom and top quartile) will be represented in the subset chosen for interviews.

Qualitative interviews with mothers will be conducted to explore perceptions around DHM use and barriers and facilitators to expressing MOM. These one-to-one, in-person semi-structured interviews will be audio-recorded and transcribed. We estimate that 15-20 interviews will be recorded although final number of interviews will be determined by thematic saturation generated through interpretation of data (38). Qualitative data will also inform whether an "RCT" design was problematic or unacceptable for mothers.

Hypothesis, sample size and power

We hypothesise that longer access to DHM (intervention) will improve the rate of breastfeeding at discharge from 35% (the rate in our NICU in 2019) to 60% (the average rate in UK NICUs using NNAP UK-wide data). Fifty-eight infants per trial group will be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive, at least 130 infants need to be recruited to complete the trial. We

estimate that up to 20% of infants may be discharged before 36 weeks ca to other neonatal units that do not have access to DHM. We will therefore need to recruit between 130 and 156 infants for the study to be powered at 80%, and we estimate this will take 18-24 months recruitment.

Analysis

Data will be analysed using an intention-to-treat approach. Additional analysis will be performed using breastfeeding outcome data for those completing the study (i.e., excluding transfers) and the first baby from a multiple pregnancy enrolled. Categorical data will be presented as counts and frequencies and will be compared using chi squared or Fisher exact test as appropriate. Morbidities will use logistic regression. Continuous data will be presented as mean (SD) or median (IQR) and the Shapiro-Wilk test will be used to test the normality of the data. Group differences in continuous data will be compared using Student's t-test or Mann-Whitney U test for normally and non-normally distributed data respectively or quantile regression as appropriate. Feeding data will be compared using multinomial statistics. All tests will be performed two tailed and $p<0.05$ will be deemed statistically significant. Qualitative data will be analysed using reflexive thematic analysis (39).

Patient and Public Involvement

The study involved discussion with parents and is aligned with the James Lind alliance priority setting that identified feeding and nutrition as key areas for research in preterm

infants. A trial steering committee including parents oversees trial conduct and progress. The trial is compliant with the UNICEF Baby Friendly Initiative.

What is already known on this topic:

MOM benefits for preterm infants are well recognised but uncertainties remain around the optimal strategy for DHM use, especially whether it impacts ~~on~~ breastfeeding. DHM is a complex intervention which has effects on infant health and maternal and healthcare staff behaviours and beliefs.

What this study adds:

This pilot RCT strives to determine if DHM provision affects breastfeeding rate at discharge and if RCT is a suitable design to answer this research question.

How this study might affect research, practice or policy:

A single RCT of a complex intervention is unlikely to resolve all uncertainties. Studies incorporating quantitative and qualitative methods may better elucidate the role of DHM in NICUs. HUMMINGBIRD may help optimise the design of future studies in larger scale.

ETHICS APPROVAL AND DISSEMINATION

Nottingham 2 Research Ethics Committee granted approval for HUMMINGBIRD Study on 6th April 2021 (IRAS Project ID 281071) and recruitment commenced on 7th June 2021. Results

will be disseminated in peer-reviewed journals and discussed with Tiny Lives Charity and Bliss UK to consider the implications of findings.

COMPETING INTERESTS

NS is the cofounder of the Human Milk Foundation, a UK charity that provides donor human milk. NE and JB report research grants paid to their institution from National Institutes for Health Research, Action Medical Research, Prolacta Biosciences US, Danone Early Life Nutrition and NeoKare but received no personal fee, and have no other financial conflicts related to industry funding. NE reports lecture honoraria from Nestle Nutrition Institute donated to charity, and Astarte Medical.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors and was supported using internal departmental funds.

AUTHORS' CONTRIBUTIONS

NE had original idea for HUMMINGBIRD after discussions with NS and played a key role in developing the protocol. JB contributed to study design and protocol development. All authors contributed to the writing and review of this paper and gave final approval for its submission.

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Not applicable.

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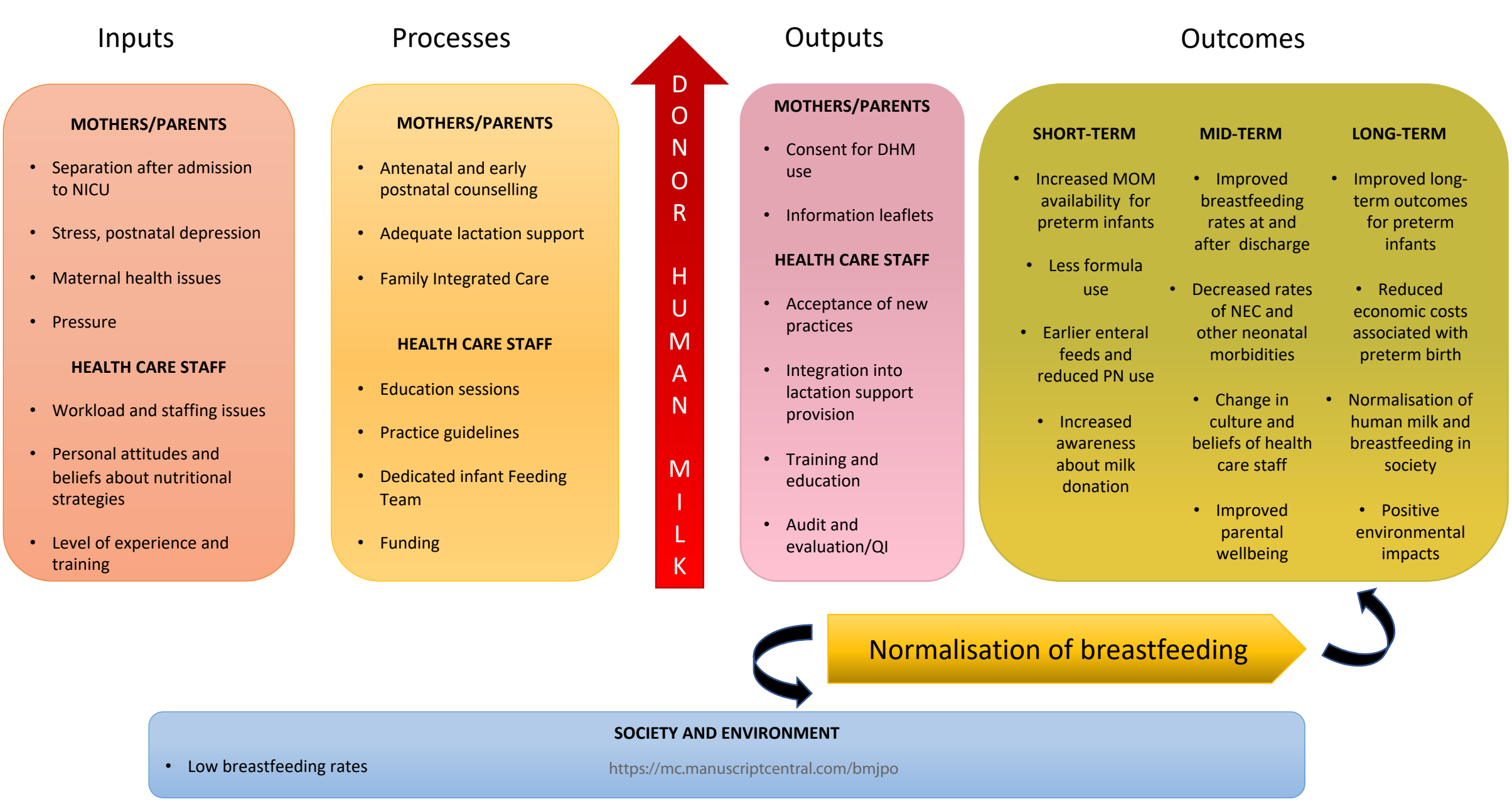
Inputs
Processes
Outputs
Outcomes
MOTHERS/PARENTS
Separation after admission to NICU
Stress, postnatal depression
Maternal health issues
Pressure
HEALTH CARE STAFF
Workload and staffing issues
Personal attitudes and beliefs about nutritional strategies
Level of experience and training
MOTHERS/PARENTS
Antenatal and early postnatal counselling
Adequate lactation support
Family Integrated Care
HEALTH CARE STAFF
Education sessions
Practice guidelines
Dedicated infant Feeding Team
Funding
DONOR HUMAN MILK
MOTHERS/PARENTS
Consent for DHM use
Information leaflets
HEALTH CARE STAFF
Acceptance of new practices
Integration into lactation support provision
Training and education
Audit and evaluation/QI
SHORT-TERM
Increased MOM availability for preterm infants
Less formula use
Earlier enteral feeds and reduced PN use
Increased awareness about milk donation
MID-TERM
Improved breastfeeding rates at and after discharge
Decreased rates of NEC and other neonatal morbidities
Change in culture and beliefs of health care staff
Improved parental wellbeing
LONG-TERM
Improved long-term outcomes for preterm infants
Reduced economic costs associated with preterm birth
Normalisation of human milk and breastfeeding in society
Positive environmental impacts
Normalisation of breastfeeding
SOCIETY AND ENVIRONMENT
Low breastfeeding rates

Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

Human Mllk, Nutrition, Growth, and Breastfeeding Rates at Discharge: The Hummingbird Study

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Human Milk, Nutrition, Growth, Breastfeeding Rates at Discharge: The Hummingbird Study

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Study proposal summary

This is the protocol proposal for a single site, non-blinded, randomised controlled trial exploring two currently used dietary regimes in preterm infants. The dietary regimes involve fully supporting mothers to provide their own expressed breast milk and using donor human milk to make up any shortfall in breastmilk supply. The primary outcome is maternal breastfeeding rates at discharge. Mothers of infants on ward 35 neonatal unit at the Royal Victoria Infirmary will be approached by clinical team members, and infants will be enrolled after signed informed consent. Infants do not undergo any additional interventions or tests, and all data used is routinely collected. Mothers will complete short questionnaires on two occasions and a subset invited to take part in qualitative interviews. The study intervention finishes at hospital discharge, but two telephone calls post-discharge will be made to ascertain duration of any prolonged breastfeeding

Title (Acronym)	Human Milk, Nutrition, Growth, and Breastfeeding Rates at Discharge: **The Hummingbird Study**
Study centre	Ward 35, Newcastle Royal Victoria Infirmary. Additional sites may be added

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Study objectives	To compare two dietary regimes that both use mother's own breastmilk and donor human milk to make up any volume shortfall
Study design	Randomised open label, controlled trial
Study population	Inclusion criteria • Preterm infants born <33 completed weeks of gestation or <1500g birthweight • Admitted to neonatal unit in first week of life • Written informed consent from parents • Maternal intention to provide breastmilk after birth Exclusion criteria • Parents unwilling to accept donor human milk • Major congenital or life-threatening abnormalities • Inability to randomise within 7 days of birth • Exposure to formula milk product prior to randomisation
Interventions	Donor human milk until full milk feeds established (control) compared to donor human milk until discharge for as long as the mother is still providing her own milk
Target number of patients	130-160 infants
Randomisation	Minimisation incorporating the following variables: gestation (<28 weeks yes/no), and twin/triplet status (yes/no) Secured, password protected web-based randomisation using minimisation algorithm (www.sealedenvelope.com or similar)
Primary outcomes	Breastfeeding at hospital discharge or 36 weeks corrected age
Secondary outcomes	Feed and growth-related outcomes Neonatal morbidities and clinical outcomes Maternal breast-feeding self-efficacy & postnatal depression scores Thematic analysis of qualitative interviews (subset)
Duration of trial intervention	36 weeks postmenstrual age or hospital discharge (which ever earlier)
Duration of study	Recruitment period: 18 months Total trial duration: 21 months

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End of Trial	Discharge from neonatal unit at Newcastle
Safety assessments	Routine assessments until discharge from Ward 35 Neonatal Unit Safety tracking during hospitalisation

Introduction

Around 10% of all births are premature, but whilst the majority do not require specialist medical treatment, those born very preterm (<32 weeks gestation) require prolonged hospital stay including intensive care. Survival in these infants has increased dramatically in recent years, but death is still common (~10% overall) as are the consequences of life-long physical and cognitive impairment.[1] In the UK around 10,000 premature infants are born every year, representing an annual cost to the NHS of ~£3 billion.[2]

The commonest cause of death or serious illness in preterm infants after the first few days are gut complications such as necrotising enterocolitis (NEC) or septicaemia.[3] Morbidity and mortality is lower in infants who receive mother's own expressed breastmilk (MOM) but >80% still require additional milk supplementation.[4] This is because there is often a 'shortfall' in maternal milk supply either due to inadequate lactation, or because mothers choose to discontinue expressing breastmilk before infants' are discharged home. Over 90% of mother's now provide at least some breastmilk, but breastfeeding rates at discharge vary considerably from 30-80% depending on hospital.[5] Low rates of breastfeeding are a major health concern, as there is strong evidence that breastfeeding throughout infancy is beneficial for cognitive and metabolic outcomes (e.g. obesity, high blood pressure etc.) in childhood and throughout the life-course.[6,7]

Use of donor human milk (DHM)

When there is a shortfall in MOM supply, an alternative milk is needed, which is either formula milk, or pasteurised, donated, human milk (DHM).[6,8] DHM is provided from one of ~12 donor milk banks in the UK which collect milk from UK donors. DHM must be tested, pasteurised, frozen and transported to hospitals for use. Because of this DHM is much more expensive (£150/litre) than formula milk (£5/litre). Studies also suggest that DHM may be less beneficial than mother's own milk at reducing neonatal disease, and strong support for mothers to provide their own milk is universally accepted.[9]

DHM has been widely used for >30 years in the NHS, but there is no national system for supply, and use varies dramatically: some clinical networks do not use it at all, whereas others provide it routinely to all preterm infants.[10] No trial has ever been powered to determine a realistic reduction on rates of necrotising enterocolitis (NEC) or sepsis and such a trial would probably need to recruit at least 2500 infants.[4] There have been no large UK trials of donor human milk in preterm infants ever, and no nationally agreed, evidenced based guidelines for use exist.[10] The only two, recent, moderately sized (300-400 infants) RCTs showed differing effects. A Canadian trial showed no improvement on the primary outcome of cognitive outcome in infancy, although NEC was lower in a secondary analysis; however, there was no impact on survival.[11,12] A larger Dutch trial showed no effect on death, NEC or sepsis (combined primary outcome) although DHM was only provided for the first 10 days of life.[13] Our current Cochrane meta-analysis concluded that there is no evidence for a reduction in death, or any long-term benefits, but whilst NEC may be lower around 33 infants would need to receive DHM to prevent one case.[4]

In the last 20 years we identified only 5 RCTs including just 1200 infants in total, of which only one study was conducted in Europe. No trials included a qualitative analysis and economic analyses was only conducted in one trial which showed no difference in costs to 18 months age. In the UK, the healthcare costs of DHM need to be considered in order to determine which infants should receive DHM. Inconsistent observational data suggest an impact of donor milk on breast feeding rates, but no trials reported the impact on continued breastfeeding at discharge.[14] Our systematic review concluded that whilst there may be an impact on breastfeeding at discharge where DHM is used (perhaps by creating a more positive culture of breastfeeding), the effect was weak and inconsistent.[15]

Whilst all neonatal units now strive to support mothers to provide breastmilk, proponents of DHM argue that it's use creates a more positive effect on mother's, as well as health professional belief and culture, will result in longer duration of breastmilk expression, and ultimately duration of breast-feeding. However, whilst there are observational data, this has never been tested in well-designed RCTs, and a recent systematic review determined the overall impact was equivocal.[15] Nevertheless, increasing numbers of women, and support groups, now advocate for universal use of DHM in vulnerable infants throughout hospital stay, despite the lack of conclusive data and high-quality health economic evaluation.[16–18]

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Current practice of DHM in the UK

Despite the widespread use of DHM, indications and practical use varies widely between Neonatal Intensive Care Units (NICUs) and hospitals. Some NICUs restrict use to only those infants born <28 weeks whereas others provide to all infants <32-34 weeks or <1500g. Some hospitals also use DHM for term born infants with cardiac and gut conditions, and in some situations, parents have asked for DHM to be used in term born infants where maternal supply is inadequate. In the first few days when milk feeds are established in preterm infants only relatively small DHM volumes are required, but volume (and therefore costs) increase as the infant grows. Clinical practice in NICUs in the UK varies widely.[10,19,20] Some NICUs only use DHM until full milk feeds have been established. This is because most key events linked to feeding (sepsis, NEC and other severe illness) occur in the first 10 days. However, other units will use DHM until closer to discharge because some clinicians feel this is more likely to support longer term breast feeding.

A further challenge arises because human breast milk alone will not meet the nutrient requirements for preterm infants.[21] To meet the higher nutrient requirements of preterm infants, commercially produced breast-milk-fortifiers (BMF) are added to mothers' own milk or donor milk. Although human milk-based fortifiers are available these are not widely used outside the USA and are very expensive.[22] BMF is therefore produced from cow's milk and is therefore a similar product to cow's milk infant formula. Many clinicians feel that rather than adding BMF to donor milk it would be preferable to use a milk formula.[20] This is because growth is slower in infants receiving DHM, and there are concerns that slow early growth may increase the risk of other problems, including worse cognitive outcomes. In addition, the continued use of DHM after full feeds are established in a typical preterm infant at 28 weeks born weighing 1000g, would cost around £1000-2000 more where the infant receives all DHM compared to infants receiving formula (in the situation where mothers do not provide any breastmilk).

Summary of key issues

In summary, use of donor human milk is commonplace in most UK neonatal units and despite the lack of a conclusive evidence base seems likely to remain a common choice for many clinicians where there is a shortfall in mothers' own milk. Most parents appear to favour use of DHM, and DHM is also strongly supported by advocacy groups including the WHO and UNICEF. There is no consistent approach to the use of DHM once feeds are established, and growth is faster when formula is used. DHM is also more expensive compared to formula. DHM may improve breastfeeding rates at discharge, and/or improve maternal self-efficacy for breast feeding, but if there are no additional

benefits from more prolonged use then resources may be better spent elsewhere, for example by employing more lactation specialists to support mothers to provide their own milk.

Proposed study to explore impacts on breastfeeding

The Hummingbird study is designed to compare two clinical dietary approaches, both of which are routinely used in the UK, by comparing the use of DHM to make up any shortfall in MOM until full feeds (control) to that of using DHM for a longer duration up to the pre-discharge period (intervention).

- **Setting**: Tertiary level NICU on ward 35, Royal Victoria
- **Population**: preterm infants <33 weeks or <1500g admitted in the first 7 days of life
- **Intervention**: use of DHM to make up any shortfall in MOM until 35-36 weeks corrected age (or the initiation of breast feeding)
- **Control**: use of DHM to make up any shortfall in MOM until full feeds are achieved (tolerating 150mls/kg/day for 48 hours) and use of preterm formula milk to make up shortfall thereafter
- **Primary outcome**: any breastfeeding at 36 weeks corrected age or hospital discharge if this is earlier. This outcome is also met if a mother is still actively expressing breastmilk which the infant receives wholly or in part via a bottle/
- **Study design**: non-blinded randomised controlled trial
- **Timeframe**: until 36 weeks corrected gestation or hospital discharge is earlier

Currently around 90-95% of our mother's start expression of breastmilk for their baby, but only 35% are still providing breastmilk at discharge compared to the national average of 60%.[5,23] The rate in the North East of England is around the lowest in the UK. Mothers who choose or are unable to continue providing MOM may do this at any point in time after they have started. Because this study is designed to impact on breastfeeding at discharge, infants in the intervention group will only continue to receive DHM if their mother is still continuing to provide breastmilk. Where the infant has not received any mother's own breastmilk for 1 week, or where the mother has told clinical staff she is no longer expressing, we will discontinue use of DHM, and the baby will receive a standard formula milk designed for preterm infants.

Secondary outcomes – growth and neonatal outcomes

We will collect a range of relevant common neonatal secondary outcomes:

1. Growth – weekly weight, length and head circumference, mid-arm/thigh where feasible, absolute changes (g/kg/day and mm/week) and change in standard deviation score

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2. Episodes of NEC, sepsis - confirmed and clinically suspected according to existing nationally agreed case definitions
3. Chronic lung disease, Retinopathy of prematurity (ROP), Intraventricular haemorrhage, Cystic PVL etc.
4. Days of intensive, high and low dependency care; age at discharge, total length of stay
5. Total volume (litres) of milk (MOM, DHM and formula) received from birth to 36 weeks
6. Age at starting fortifier
7. Type of feeding at discharge (direct breast feeding, tube feeding etc.)

Secondary outcomes – breastfeeding self-efficacy and thematic analysis of interviews

We will use a mixed methods approach to determine maternal breastfeeding self-efficacy expression and conduct qualitative interviews in a subset of up to 20 mothers. We will use two short validated questionnaires – the Breast-feeding Self-efficacy Scale – Short form (BSES-SF)[24,25] and the Edinburgh Postnatal Depression Scale[26] - at two time points: between 5-10 days of age and again at 35-36wca or prior to discharge if sooner. These only take around 1-2 minutes to complete. We will use the BSES-SF scores to identify women in the top and bottom quartiles of scores and invite up to 10 women per trial group to take part in a qualitative tape-recorded interview. This will be transcribed and analysed using thematic analysis. We will develop a topic guide based on the questions on the BSE-SF and our experience (see appendix). Interviews will be conducted by a single member of the research team (KC) shortly before or after hospital discharge. We will seek consent to keep in touch with parents after discharge. We will also ask for consent to keep in telephone contact with mothers who are breastfeeding at discharge at 1-2 monthly intervals in order to simply ascertain duration of breastfeeding.

Sample size and Power

We hypothesise that prolonged use of DHM will improve the rate of breastfeeding at discharge from 35% to the UK national average of 60%. Fifty-eight infants per trial group would be required to detect an improvement in breastfeeding rates at discharge from 35% to 60%. Assuming 10% of infants do not survive we will need to recruit at least 130 infants who are still receiving care at the RVI at ~36 weeks corrected age (wca). We estimate that up to 20% of infants may be discharged before 36wca to a local hospital that does not have continued access to DHM. We will therefore need to recruit between 130 and 156 infants in order that we are powered to determine the primary outcome. The NICU on ward 35 admits ~160 babies every year <1500g or <33 weeks of whom we expected around 80% of infants will be enrolled (based on previous RCTs we conducted). Therefore, we estimate we will need a 12-18 months recruitment period so we can enrol at least 130 infants who achieve the primary outcome. Twins and triplets will be co-randomised to the same trial arm. We will analyse the data for all infants

using an intention-to-treat approach, but we will perform additional analysis only using breastfeeding outcome data for the first twin enrolled.

Funding

This trial will use dietary treatments already used in this way on the neonatal unit and collect routinely available electronic clinical data extracted from e-record and Badger neonatal database and inputted into an excel worksheet. There are no costs for use of questionnaires. Trial recruitment, consenting and interviews will be conducted by a member of clinical staff who has time available as part of daily activities (KC) supported by the neonatal research nurse. Costs for ISRCTN registration, printing, paperwork, tape recording, transcription, and travel costs for membership of the TSC will be met out of existing departmental research funds.

Trial registration, Ethics, HRA and risk burden

The trial will be registered on ISRCTN prior to opening. We will apply for HRA and REC approvals and apply for adoption onto the NIHR portfolio. There are no specific ethical issues with this trial, but we recognise the additional burden placed on parents by being asked to consider trial enrolment. There are no additional safety issues as part of the trial per se Use of donor breastmilk could be associated with theoretical risks (although none have been documented) or inadvertent use of the 'wrong' milk, but donor milk is already used in routine practice and this trial does not increase the risk. No additional interventions or tests are applied to infants as part of the trial. The questionnaires do ask sensitive information but only members of the clinical team will see the responses and will already be aware of important family and mental health issues as part of routine family centred care on the neonatal unit. Where the mother wishes, we will use the questionnaire responses to provide further targeted support to help her. The trial is fully compliant with national recommendations and Baby Friendly Initiative (BFI) part of UNICEF.

Patient Public Involvement and importance to the NHS

We have discussed this study with parents on the neonatal unit, and other parents after discharge. Parents tell us that the risks and complication associated with feeding preterm infants, and the stress of being able to provide breastmilk for their infant are very important issues. In addition, the James Lind alliance (JLA) priority setting www.jla.nihr.ac.uk/priority-setting-partnerships/preterm-birth/top-10-priorities/ identifies feeding and nutrition as very important. Our study focuses on key JLA priorities (i) what is the optimum milk feeding strategy (ii) what type of support is most effective in improving breastfeeding and will provide additional information relevant for a further 2 additional priorities (iii) how can infection be better prevented (iv) what interventions are most effective at preventing NEC. This trial is of major relevance to the NHS and studies interventions and outcomes highlighted in a recent top research priority setting in preterm infants.[27] Breastfeeding is a major national priority and

is an intervention that has potential to benefit marginalised and poorly resourced groups. Breastfeeding support in the community is essential to continued successful breastfeeding but is recognised as being inadequate in many settings. NEC is a devastating condition, and half of the infants requiring surgery die or have long-term serious disability. Donor human milk is an important cost for the NHS, but the total costs of DHM even for a large NICU will still be substantially less than the costs associated with a single episode of surgical NEC. We will invite a parent to join the TSC and invite an additional independent member to the TSC from a charity or parent advocacy organisation. We will liaise with Tiny Lives charity and Bliss UK to consider the implications of our trial findings and disseminate the results.

Experience of research team members

We are an experienced research team, having recruited more than 1000 preterm infants to trials and studies in the last 10 years, including qualitative exploration of sensitive issue in parents whose babies did not survive. We are recognised internationally for our work on feeding and nutrition, and associated complications such as necrotising enterocolitis. We have worked closely with parents on all our studies (see above).

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Appendix 1: Breastfeeding Self-Efficacy Scale – Short Form

[24]Wheeler et al. 2013

Original Items

I can….

1. Determine that my baby is getting enough milk
2. Successfully cope with the breastfeeding situation (pumping and actual breastfeeding) like I have with other challenging tasks
3. Breastfeed my baby without using formula as a supplement
4. Ensure that my baby is properly latched on for the whole feeding
5. Manage the breastfeeding situation to my satisfaction
6. Manage to breastfeed even if my baby is crying
7. Keep wanting to breastfeed
8. Comfortably breastfeed with my family members present
9. Be satisfied with my breastfeeding experience
10. Deal with the fact that pumping and breastfeeding can be time consuming
11. Finish feeding my baby on one breast before switching to the other breast
12. Continue to breastfeed my baby for every feeding
13. Manage to keep up with my baby's breastfeeding demands
14. Tell when my baby is finished breastfeeding

Additional Items

1. Pump enough milk for my baby
2. Get help with breastfeeding if or when I need it
3. Determine when my baby needs to be fed
4. Switch from mostly pumping to mostly or completely breastfeeding my baby

Appendix 2: Edinburgh Postnatal Depression Scale (EPDS)

[26]Cox et al.

 I have been able to laugh and see the funny side of things.

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- ◉ As much as I always could
- ○ Not quite so much now
- ○ Definitely not so much now
- ○ Not at all

I have looked forward with enjoyment to things.

- ○ As much as I ever did
- ○ Rather less than I used to
- ○ Definitely less than I used to
- ○ Hardly at all

I have blamed myself unnecessarily when things went wrong.

- ○ Yes, most of the time
- ○ Yes, some of the time
- ○ Not very often
- ○ No, never

I have been anxious or worried for no good reason.

- ○ No not at all
- ○ Hardly ever
- ○ Yes, sometimes
- ○ Yes, very often

I have felt scared or panicky for no very good reason.

- ○ Yes, quite a lot

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- Yes, sometimes
- No, not much
- No, not at all

 Things have been getting on top of me.

- Yes, most of the time I haven't been able to cope at all
- Yes, sometimes I haven't been coping as well as usual
- No, most of the time I have coped quite well
- No, I have been coping as well as ever

 I have been so unhappy that I have had difficulty sleeping.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

 I have felt sad or miserable.

- Yes, most of the time
- Yes, sometimes
- Not very often
- No, not at all

 I have been so unhappy that I have been crying.

- Yes, most of the time
- Yes, quite often

- Only occasionally
- No, never

The thought of harming myself has occurred to me.

- Yes, quite often
- Sometimes
- Hardly ever
- Never

Appendix 3: data items

We will use standard definitions of disease and outcomes refined and validated in our previous studies to collect data including

- Standardized forms for: NEC/gut complications; sepsis; ROP grade and treatment at discharge; CLD at 36w; presence of IVH/PVL or PDA requiring treatment
- Day of first milk feed; receipt of buccal colostrum
- Time to full feeds sustained for 3 days; days of nil by mouth; age at first use of DHM, fortifier and formula milk
- Postnatal age at last breastmilk expression, first day of feeding from the breast, postnatal age at last received MOM, age at last breast feed (telephone report post-discharge)
- Maternal demographics: postcode/SES, age, parity, previous breastfeeding, previous breastfeeding for at least 3 months, smoking, major maternal disease e.g. diabetes etc.
- Validated questionnaire for breastfeeding self-efficacy (BSES)
- Validated questionnaire Edinburgh postnatal depression score (EPND)
- Costs associated with length of stay (days) for each category of care (intensive, high and low dependency) estimated using NHS HRGs
- Costs of DHM provided by Hearts Milk Bank includes transport, storage at site etc.

Appendix 4: Topic guide for interviews

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Parent Topic Guide for Interviews

Interviewer extends a special thanks to the mother for agreeing to take part in the research. Explain that the aims of the study are to seek the views and experiences about aspects of breastfeeding support and use of human donor milk. Reassure that it is OK for anyone else, including the father, to be present if the mother wishes. Make the point that she doesn't have to answer all questions.

Interviewer introduces herself and outlines the study

Explain use of the audio recorder – the interview is being audio recorded so I have an accurate account of what the participant has said and so that I don't have to take handwritten notes. Interviews will be anonymised when they are typed up prior to analysis (i.e. their names and any other information that could identify them are taken out.)

- Assure confidentiality.
- Ask whether they have any more questions about the study?
- Check they have signed the consent form and are happy
- Explain that the interview can be ended or postponed at any time.

Introduction

Can you tell me a little about how your baby is getting on at present?

Feelings and support before and after birth

- Did you think about breastfeeding before your baby was born?
- Have you breast fed before, or been to any antenatal classes on breastfeeding?
- Did having a premature baby change what you thought or felt?

Patient Information

- Did anyone speak to you about expressing breastmilk shortly after the birth?
- Do you think you were given enough information or support?
- Did you feel empowered to make an informed decision or did you feel pressurised?
- In what ways could the information or support you were given be improved?
    - explanations
    - information to read
    - other?

Feelings and support whilst on the NICU

- Do you think the staff were sensitive to your opinions and any challenges you had?
- What could staff have done to improve support for you?
- Did you feel supported by friends, partners and other family members?
- Looking back, how do you feel your experience of providing breastmilk was for this baby?
- What do you think about the use of human donor milk or formula milk?
- Would you have preferred your baby to receive donor milk for longer?
- If money (NHS costs) was not an issue, do you think other babies should be offered donor milk if the mum is struggling to breast feed? E.g. a term baby where the mother is unwell, or has a poor milk supply?

End of interview

I have reached the end of my questions. Is there anything you would like to add?

How did you feel about the interview?

- Are there any questions you would like to ask me about the study?
- Thank them for giving up their time and supporting the study.
- Ask them if they still agree for the interview to be analysed.

Explain they can find a summary of the findings on the website www.neonatalresearch.net at the end of the study.