

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



Human Milk, Nutrition, Growth, and 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

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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	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • 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 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • 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	<p>Feed and growth-related outcomes</p> <p>Neonatal morbidities and clinical outcomes</p> <p>Maternal breast-feeding self-efficacy & postnatal depression scores</p> <p>Thematic analysis of qualitative interviews (subset)</p>
Duration of trial intervention	36 weeks postmenstrual age or hospital discharge (which ever earlier)
Duration of study	<p>Recruitment period: 18 months</p> <p>Total trial duration: 21 months</p>

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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 breastfeeding. 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

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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 Scale²⁶ - 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

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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

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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

²⁴Wheeler 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)

²⁶Cox 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

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- 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.

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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.