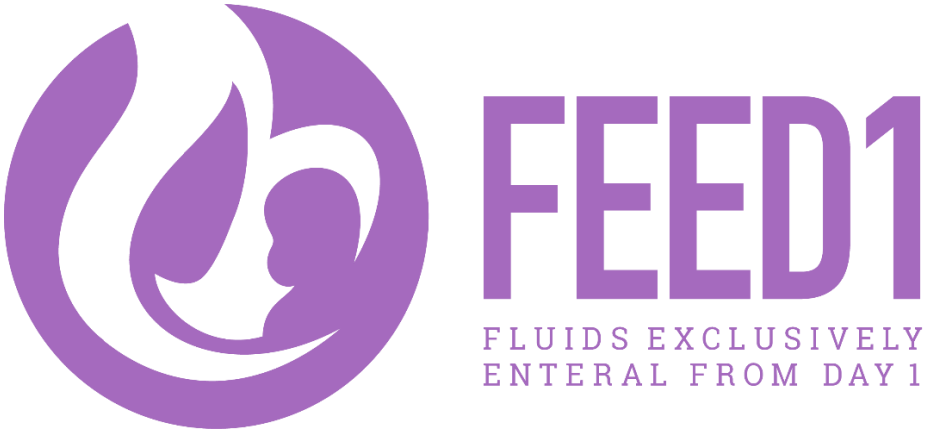
TRIAL PROTOCOL



A randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age)

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Protocol development and sign off

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Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1		1.3	Non-substantial	(i) Clarification of wording for some secondary outcomes. (ii) Correction of stop/go criteria thresholds. (iii) Update to co-applicant

				details. (iv) Clarification of SWAT intervention.

CI Signature Page	
This protocol has been approved by:	
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Protocol Version Number:	Version: 1.3
Protocol Version Date:	14-May-2020 (dd-mmm-yyyy)
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TRIAL SUMMARY

Title: A randomised controlled trial of full milk feeds versus intravenous nutrition with gradual feeding for preterm infants (30-33 weeks gestational age)

Trial Design: Multi-centre, open, parallel, randomised controlled, superiority trial

Objective: To investigate whether, in infants born at 30^{+0} to 32^{+6} weeks (inclusive) gestation, full milk feeds initiated in the first 24 hours after birth reduce the length of hospital stay in comparison to intravenous (IV) fluids with gradual milk feeding.

Participant Population and Key Eligibility Criteria: Infants will be eligible if born between 30^{+0} to 32^{+6} weeks (inclusive) gestation and are $\leq$3 hours of birth. Exclusion criteria include infants with known congenital abnormalities of the gastrointestinal tract or conditions that make enteral feeding unsafe, reversed end-diastolic flow on antenatal umbilical Doppler ultrasound.

Intervention: Full milk feeding from day one, with daily fluid volume given as milk starting at a minimum of 60ml/kg/day and increased as per usual local practice for fluid volume.

Control: Parenteral nutrition/intravenous fluids with gradual milk feeding as per usual local practice.

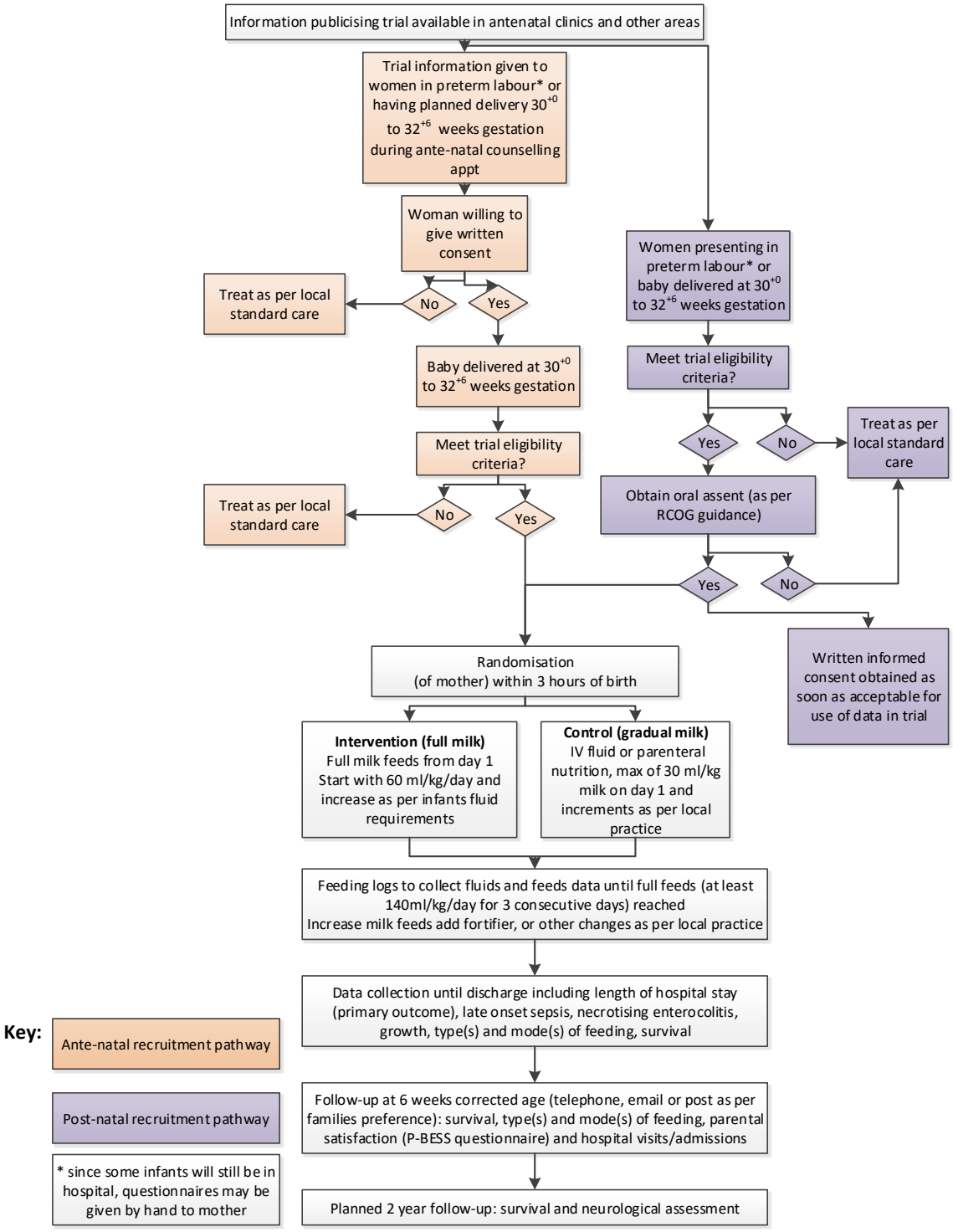
Primary outcome: length of hospital stay
Secondary outcomes:

- Survival to hospital discharge
- Survival to 6 weeks corrected gestational age (i.e. term gestation + 6 weeks)
- Incidence of microbiologically-confirmed (positive blood/cerebrospinal fluid [CSF] culture) or clinically suspected (defined by diagnostic criteria[1]) late-onset sepsis until hospital discharge
- Necrotising enterocolitis (Bell's stage 2 or 3[2]) until hospital discharge
- Time taken to maintain full milk feeding (defined as at least 140 ml/kg/d for three consecutive days)
- Time to regain birth weight
- Growth (z scores for gestational age at hospital discharge (as per UK-NICM growth charts) –
    - weight
    - length
    - head circumference
- Breast-feeding at hospital discharge
- Mother's breast milk fed at hospital discharge
- Number of days of peripheral cannula until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved
- Number of IV cannulae inserted until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved
- Number of days of parenteral nutrition, until hospital discharge
- Number of central venous lines inserted (including umbilical and percutaneous or surgically inserted venous lines) until hospital discharge
- Number of central line days until hospital discharge
- Time until objective discharge criteria are met (see section 2.2.1)
- Hospital visits (including day care and overnight admissions) up to 6 weeks of corrected age (i.e. term gestation + 6 weeks)
- Breast-feeding at 6 weeks of corrected age (i.e. term gestation + 6 weeks)
- Mother's breast milk fed at 6 weeks of corrected age (i.e. term gestation + 6 weeks)

- Parental satisfaction and wellbeing at 6 weeks of corrected age (i.e. term gestation + 6 weeks), using the Preterm Birth Experience and Satisfaction Scale (p-BESS) questionnaire[3].
- Retinopathy of prematurity at discharge
- Chronic lung disease until discharge
- Brain injury on imaging until discharge

Sample size: 2088 infants requiring recruitment of 1770 women

Figure 1. Participant Flow Diagram:



*women presenting in preterm labour may be consented via the antenatal or postnatal pathway. Clinician discretion will be used to determine the most appropriate method.

TABLE OF CONTENTS

Abbreviations and Definitions

Definitions

Term	Description
Abbreviations	
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AR	Adverse reaction
BERC	Blinded endpoint review committee
CI	Chief investigator
COIN	Core Outcomes in Neonatology
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSF	Cerebrospinal fluid
CV	Curriculum vitae
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EU GDPR	European Union General Data Protection Regulation
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous
LNU	Local Neonatal Unit
LOS	Late-onset sepsis
NCTU	Nottingham Clinical Trials Unit
NEC	Necrotising enterocolitis
NHS	National Health Service
NICM	Neonatal and Infant Close Monitoring
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health Research
NNRD	National Neonatal Research Database
NRES	National Research Ethics Service
p-BESS	Preterm Birth Experience and Satisfaction Scale
PI	Principal Investigator
PIS	Patient Information Sheet
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee

SAE	Serious Adverse Event
SIV	Site Initiation Visit
SSNAP	The Oxford Support for Sick Newborn and their Parents
SWAT	Study within a Trial
TAMBA	Twins and Multiple Births Association
TSC	Trial Steering Committee
UNICEF	United Nations International Children's Emergency Fund
Definitions	
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with the treatment received. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a treatment, whether or not related to the treatment.
Related Event	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event (SAE)	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator** Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious
Unexpected and Related Event	An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event	The type of event that is not listed in the protocol as an expected occurrence.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial

1. Background and Rationale

1.1. Background

In preterm infants, early establishment of enteral feeding is associated with reduced sepsis, improved growth[4], and enhanced neurodevelopment[5]. Achieving full milk feeds sooner and improving growth without infection or necrotising enterocolitis (NEC) may help the infant be ready for home earlier, reducing the duration of hospital stay. Despite evidence to the contrary[6], clinicians often delay initiating feeds or increment feeds slowly due to fear of NEC. The recently completed Speed of Increasing milk Feeds Trial (SIFT) provides firm evidence from over 2,800 infants that faster advancement of milk feeds does not increase the risk of NEC even in the most premature infants [3]. In this large, multi-centre trial comparing fast (30ml/kg/d) vs. slow (18ml/kg/d) feed increments in 2804 infants born before 32 weeks gestation, the risks of NEC or death were not increased by the faster increment in feeds. Faster fed infants achieved full feeds quicker and received less intravenous (IV) nutrition. The recent Cochrane review assessing advancement of feed volumes in preterm infants concluded that advancing the volume of enteral feeds at a slow rate results in several days of delay in establishing milk feeds and may increase the risk of invasive infection[4].

These results indicate that there may be benefit from a faster approach, in infants between 30^{+0} to 32^{+6} weeks by providing their full fluid requirements solely as enteral feeds. This can be achieved by providing all the fluid requirements as milk from day 1 without using IV fluids or parenteral nutrition i.e. “full milk” feeds from the day of birth. There are only two small, underpowered studies that have investigated this strategy. One study randomised 64 infants (mean gestation 31 weeks) to an intervention group that received full milk from birth and a control group that received parenteral nutrition and feed increments at 20ml/kg/day[7] showing reduced length of stay in the full milk group. Similarly, Sanghvi[8] conducted a small study in 46 infants (birth weight 1200-1500 grams; mean gestation 31 weeks) who were randomised to receive full milk from 1 hour after birth or IV fluids and slow feed increments (20ml/kg/d). They found that infants randomised to full milk, regained birth weight quicker, had improved growth at discharge, shorter duration of hospital stay, and fewer cases of sepsis without an increased risk of NEC. These findings suggest it is potentially safe and may be better to start full milk feeds on day 1 without increasing the risk of NEC and possibly reducing the risk of sepsis. An observational study also showed that implementing full milk feeds from birth is feasible and acceptable, with the infants on full milk having significantly fewer cases of NEC and sepsis, less antibiotics, less parenteral nutrition, and a shorter average hospital stay[9]. These studies were all conducted in India where the preterm population, healthcare resources, infrastructure and delivery systems as well as treatments and risk factors are different to that in the UK. There have been no studies in the UK or other similar high resource setting investigating the strategy of feeding preterm infants “full milk” feeds from day 1.

1.2. Trial Rationale

1.2.1. Justification for participant population

Health need: This research is important due to the large number of infants and families that could benefit if FEED1 shows that full milk feeds from day 1 can reduce length of hospital stay and painful interventions, such as IV cannulation for intravenous fluids and nutrition. Parents have told us that these outcomes and normalisation of care are very important to them.

FEED1 will address a NHS England priority of improving patient experience and ensuring patient safety via an intervention that could reduce painful interventions, lessen the risk of infection, and enhance family wellbeing through greater parent involvement in the care of their infants and shortening the length of hospital stay. In keeping with the NHS Business Plan for 2016/17, FEED1 has the potential to deliver reductions in spending through the NHS ‘Right Care’ programme[10].

As part of the NHS planning guidance for 2016/17, the NHS England document “Improving Value for Patients from Specialised Care” supports a framework that encourages “the right baby in the right place at the right time”[11]. The service specification for Neonatal Critical care states that each Operational Delivery Network should have the capacity to provide neonatal care for at least 95% of infants born to women booked for delivery in the network[12]. Due to their large numbers (over 6000 infants in England and Wales per year), even a modest decrease in hospital stay of 30 to 33 week infants would produce an important increase in cot capacity in neonatal units. At a cost of approximately £450 per day, reducing hospital stay by just a single day per infant would amount to £2.8 million annual savings from the 6,308 infants born at 30 to 33 weeks gestation in the UK. In addition to the cost to the health service, preterm birth and prolonged hospital stay are also financial stressors for families. The Bliss report in 2014 “It is not a game: the very real cost of having a premature or sick baby” estimated that parents spend £282 per week in addition to loss of working days when their preterm infant is in the hospital[13]. Reduction in hospital stay would reduce this stress.

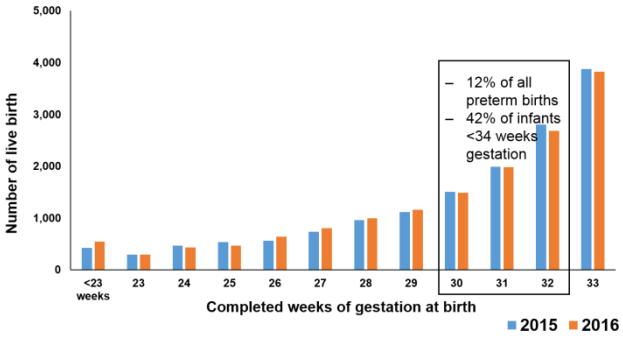


Figure 2. Live birth by gestational age in England and Wales

In 2016, in England and Wales, there were 694,427 live births of which 54,143 (7.8%) were preterm (born before 37 completed weeks gestation). Providing optimal nutrition is a cornerstone of neonatal care and the subject of many recent research studies including SIFT[14], ADEPT[15], NEON[16] and SCAMP[17]. These and other similar studies focus on extremely preterm infants (born before 30 weeks) at highest risk of adverse outcomes (death or NEC). However, more than 90% of preterm infants are born at or after 30 weeks, including the 12% of preterm infants who are eligible for FEED1.

More mature preterm infants (≥ 34 weeks) typically, do not require special care. Infants born at 30, 31 or 32 weeks comprise over 40% of preterm infants admitted to neonatal units (Figure 2) (in 2016 there were 6159 infants in this group in England and Wales) and form the largest proportion of workload for neonatal services.

Treatments that reduce length of stay in this group of preterm infants could therefore impact the largest number of infants in neonatal units. Infants that are fully milk fed need less monitoring and can be moved to lower dependency care, making them ready for home sooner and reducing the length of hospital stay. This would make available scarce higher dependency cots for sicker infants and avoid transferring infants further afield to access resources.

Strategies that aim to safely achieve a shorter hospital stay could improve care for all infants who require neonatal care. Full milk feeds may also reduce the cost of care by decreasing use of parenteral nutrition, IV fluids, and reducing iatrogenic infections. Preterm birth is associated with long term morbidities and large lifetime financial costs, placing strain on NHS finances and social care resources. Full milk feeds may improve nutrition and reduce morbidities such as sepsis, thereby improving neurodevelopmental outcome and lifelong quality of life for this large group of infants. Such an approach that improves the care of preterm infants while simultaneously reducing the cost of care would achieve the NHS "Five Year Forward View" aim of achieving efficiency savings while maintaining and improving quality of care and safety[19]. There are also potential benefits for mothers

and families from a less medical model of care, with opportunities for involvement in care, improved satisfaction and mental health outcomes.

FEED1 addresses three of the top six research priorities identified by the James Lind Alliance[20]:

• "What is the optimum milk feeding strategy and guidance (including quantity and speed of feeding and use of donor and formula milk) for the best long-term outcomes of premature infants?
• How can infection in preterm infants be better prevented?
• Which interventions are most effective to prevent necrotising enterocolitis in premature infants?"

Utilising the Bliss network, we conducted an online survey of UK parents whose infants were born between 30 to 33 weeks gestation and had spent time on the neonatal unit in the last 5 years. We received 334 responses in under one week (246 in <24 hours) indicating the question's importance. 86% of women said that full milk feeds from birth would be acceptable to them. 55% said they would be willing to participate in a research study which involved their baby being randomised to full milk feeds from birth or slower introduction. Of those who said they would be unwilling to participate, the majority (76%) declined because they had a preference for full milk feeds from birth. Mothers participating in the survey were not aware that this would not be offered to infants outside of the trial, as usual current practice is to start infants on IV fluids and introduce milk gradually. This study has been developed following the SIFT trial which finished recruitment 11 months ahead of target. We expect that this question is also one that parents and clinicians will wish to provide evidence for.

Between 01 May and 09 May 2018, we conducted a survey of neonatologists and neonatal dietitians in the UK to explore their interest in the proposed trial. We received 42 responses in less than 7 days. All respondents agreed that this is an important research question. The survey confirmed our previous published findings that infants in the 30-33 weeks gestation group are not given full milk feeds on day 1[21]. Twenty-six of the 42 hospitals have donor breast milk available and 32 are UNICEF Baby Friendly accredited. Twenty-nine of the 42 respondents were willing to randomise to this trial. Among those who were unwilling to randomise, 6 said they would not be happy randomising certain infants to full milk while 2 said they would not be willing to randomise certain infants to gradual milk feeds. Among the other reasons, two respondents said they would need to discuss with other team members before agreeing to participate. Five respondents raised the issue of not wanting to give any milk other than mother's own breast milk and that randomisation to full milk would mean the infant receives some form of supplement for the first few days. It is unlikely that mothers who deliver preterm will be able to express breast milk in sufficient volume to provide full milk feeds on the first few days of life. In current practice, to supplement breast milk, preterm infants are given intravenous fluids or parenteral nutrition. In the intervention arm of this study, infants will instead receive donor human milk or preterm formula as a replacement of intravenous fluid. This is further described in Section 11. The study will stress the importance of mother's own milk feeding and breast-feeding support will be provided to mothers in both arms of the trial. If the volume of mother's milk is insufficient, which is likely to occur in the first few days, supplemental milk will be given instead of the usual supplemental intravenous fluids and mother's milk feeding will continue with full encouragement and support.

To provide sufficient power to assess outcomes of NEC and sepsis, discussions are ongoing to set up parallel studies in other countries such as Canada and Australia. These outcomes occurred in 1% and 12% of infants respectively in SIFT who would have been eligible for FEED1.

In summary, a more streamlined and safe feeding approach for preterm infants that is acceptable and effective in the UK offers improved outcomes for this large group of infants and their families,

reducing cost of care and enhancing the efficiency of neonatal services. Although there are some small studies, there is insufficient evidence to change practice and we propose a randomised controlled trial to determine if the strategy of full milk feeding from birth can achieve these benefits.

1.2.2. Justification for design

This trial is a multi-centre, open, parallel, randomised controlled superiority trial.
Blinding of both investigators and families is not possible due to the nature of the intervention. As a consequence, and to support the potentially subjective primary outcome, a secondary outcome will assess the time until the objective discharge criteria are met. This secondary outcome will be determined by outcome assessors blinded to treatment allocation, and is intended to remove any subjective bias that may be present in the clinician's decision to discharge an infant, due to their knowledge of the infant's treatment allocation. Central, blind adjudication will also be used to determine the secondary outcomes of NEC and late onset sepsis.

1.2.3. Choice of treatment

Full milk feeds vs. parenteral nutrition/intravenous fluids with gradual milk feeding as per usual local practice.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

To investigate whether, in infants born at 30^{+0} to 32^{+6} weeks^{+days} (inclusive) gestation, full milk feeds initiated in the first 24 hours of life reduce the length of hospital stay in comparison to IV fluids with gradual milk feeding.

Population:	infants born at 30^{+0} to 32^{+6} weeks (inclusive) gestation
Intervention:	full milk feeding from day one
Comparator:	parenteral nutrition/intravenous fluids with gradual milk feeding as per usual local practice
Primary Outcome:	length of hospital stay
Secondary Outcomes:	secondary outcomes as detailed in section 2.2

2.2. Outcome Measures

Primary outcome: Length of hospital stay
Secondary outcomes:

- Survival to hospital discharge
- Survival to 6 weeks corrected gestational age (i.e. term gestation + 6 weeks)
- Incidence of microbiologically-confirmed (positive blood/cerebrospinal fluid [CSF] culture) or clinically suspected (defined by diagnostic criteria[1]) late-onset sepsis until hospital discharge
- Necrotising enterocolitis (Bell's stage 2 or 3[2]) until hospital discharge
- Time taken to maintain full milk feeding (defined as at least 140 ml/kg/d for three consecutive days)
- Time to regain birth weight
- Growth (z scores for gestational age at hospital discharge (as per UK-NICM growth charts))
    - weight
    - length
    - head circumference
- Breast-feeding at hospital discharge
- Mother's breast milk fed at hospital discharge
- Number of days of peripheral cannula until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved

- Number of IV cannulae inserted until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved
- Number of days of parenteral nutrition, until hospital discharge
- Number of central venous lines inserted (including umbilical and percutaneous or surgically inserted venous lines) until hospital discharge
- Number of central line days until hospital discharge
- Time until objective discharge criteria are met (see section 2.2.1)
- Hospital visits (including day care and overnight admissions) up to 6 weeks of corrected age (i.e. term gestation + 6 weeks)
- Breast-feeding at 6 weeks of corrected age (i.e. term gestation + 6 weeks)
- Mother's breast milk fed at 6 weeks of corrected age (i.e. term gestation + 6 weeks)
- Parental satisfaction and wellbeing at 6 weeks of corrected age (i.e. term gestation + 6 weeks), using the Preterm Birth Experience and Satisfaction Scale (p-BESS) questionnaire[3].
- Retinopathy of prematurity until discharge
- Chronic lung disease until discharge
- Brain injury on imaging until discharge

The selection of the outcome measures has been guided by the Core Outcomes in Neonatology (COIN) core outcome set, developed by a steering committee comprised of parents and former patients, healthcare professionals and researchers[22].

Data on retinopathy of prematurity (ROP) will be collected and reported descriptively for those participating infants who are eligible for ROP screening according to the national screening criteria[23].

A subsequent funding application will be submitted to extend the scope of this trial to follow-up infants at 2 years of corrected gestational age. We intend to compare data on survival to 2 years of age and neurodevelopmental impairment including the remaining COIN outcomes (general gross motor ability, general cognitive ability, visual impairment or blindness, hearing impairment or deafness).

Definition of Microbiologically-confirmed Late-onset Invasive Infection (LOS)[1]

A modified version of the UK Neonatal Infection Surveillance Network case-definition will be used: Microbiological culture from blood or CSF sampled aseptically more than 72 hours after birth of any of the following:

- potentially pathogenic bacteria (including coagulase-negative Staphylococci species but excluding probable skin contaminants such as diptheroids, micrococci, propionibacteria or a mixed flora
- fungi

AND

Treatment for 5 or more days with intravenous antibiotics after the above investigation was undertaken. If the infant died, was discharged, or was transferred prior to the completion of 5 days of intravenous antibiotics, this condition would still be met if the intention was to treat for 5 or more days.

There is no need to report urinary tract infection unless there is also a positive blood culture.

Definition of Clinically Suspected Late-onset Invasive Infection[24]

This is adapted from the European Medicines Agency consensus criteria and the predictive model. Either – absence of positive microbiological culture OR culture of a mixed microbial flora or of likely skin contaminants (diptheroids, micrococci, propionibacteria) only

AND

Clinician intent to administer intravenous antibiotic treatment for 5 or more days (excluding antimicrobial prohylaxsis) for an infant who demonstrates 3 or more of the following clinical or

laboratory features of invasive infection:

- Increase in oxygen requirement or ventilatory support
- Increase in frequency of episodes of bradycardia or apnoea
- Temperature instability
- Ileus or enteral feeds intolerance and/or abdominal distention
- Reduced urine output to <1ml/kg/hour
- Impaired peripheral perfusion (impaired capillary refill time >3 seconds, skin mottling or core-peripheral temperature gap >2°C)
- Hypotension (clinician defined as needing volume or inotrope support)
- "irritability, lethargy or hypotonia" (clinician defined)
- Serum C-reactive protein levels to >15 mg/L or procalcitonin ≥2mg/ml
- White blood cells count <4 or >20 X 10^9 cells/L or platelet count <100X10^9/L
- Glucose intolerance (blood glucose <2.2 mmo/l or >10 mmol/l)
- Metabolic acidosis (base excess <-10mmol/L or lactate>2mmol/L)

2.2.1. Objective discharge criteria

Data will be collected on a daily basis to ascertain whether the infant has been weighed, whether the infant is able to take at least one full suck feed and whether the infant has been on any temperature support. These data will be used in a secondary outcome of 'discharge readiness' using the assessment of the date at which each infant first met all three of the below discharge criteria. This assessment will be carried out by the study statistician who will be blinded to treatment allocation:

- Current weight ≥ 1700 grams
- Infant is able to take at least one full suck feed which is assessed as adequate (for example not needing further feeds within 3 hours)
- Temperature control: infant has been off all additional temperature support for at least 24 hours.

3. Trial Design and Setting

3.1. Trial Design

Multi-centre, open, parallel, randomised controlled, superiority trial. Recruitment of 1770 women is required in order to collect outcome data on 2088 infants (accounting for multiple births) in order to achieve the trial objectives. Women will be randomised on a 1:1 allocation ratio. Further information on sample size and randomisation is found in subsequent sections of this protocol.

3.2. Trial Setting

Mothers and their infants will be recruited primarily from hospitals in the UK who have either;

- Level 3 facilities i.e. Neonatal Intensive Care Unit (NICU)
- Level 2 facilities i.e. Local neonatal unit (LNU)

Hospitals with Level 1 neonatal facilities may still be considered for participation in the trial, depending on the size of the unit and number of potentially eligible infants.

The trial will be promoted in antenatal clinics and wards using posters and leaflets. In addition, the trial will be publicised via Bliss, the UK's largest charity for infants who are born premature or sick, and other organisations/groups who are relevant to the premature infant population. Publicity will be via media such as (but not limited to) flyers, posters, websites and social media platforms.

The trial has two recruitment pathways, depending on the time point at which the woman is first approached about the trial. Where possible, women will be approached antenatally and given trial information during the antenatal counselling visit routinely undertaken by a neonatologist when a pregnancy is expected to result in preterm birth. Some births will be too unpredictable or rapid for women to be approached antenatally and therefore these women will be approached within 3 hours of birth, using the oral-assent pathway. Further details are given in section 5.

The two pathways described in the above paragraph are shown in further detail on the participant flow diagram, found in Figure 1.

4. Eligibility

4.1. Inclusion Criteria

1. Infant born at 30 weeks + 0 days to 32 weeks + 6 days gestation, inclusive
2. Infant <3 hours (180 minutes) old (since recorded time of birth)

Infants requiring respiratory support (such as via continuous positive airway pressure) or other supportive treatments will be included in the study if the attending clinician is in equipoise about the infant being randomised to either the "full milk" or the "gradual milk" arm. Similarly, well infants should only be included if the attending clinician is in equipoise about the best feeding regime and the infant being randomised to either "full milk" or "gradual milk" groups.

4.2. Exclusion Criteria

1. Infant with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe
2. Infant who are small for gestational age (birth weight <10th centile) AND evidence of reversed end-diastolic flow on antenatal umbilical artery Doppler ultrasound*
3. Mother has participated in the trial during a previous pregnancy#

*Small for gestational age infants with antenatal Doppler ultrasound scan showing absent umbilical artery flow or whose mother's did not have antenatal umbilical Doppler ultrasound may be eligible for the trial if they meet the other inclusion criteria.

#The trial will recruit over 36 months. It is possible that the mother of an infant(s) who has already participated in the trial has another pregnancy in this duration. In such circumstances, the infant(s) born in subsequent pregnancies will be excluded to avoid bias due to the experience of previous participation.

5. Consent

The study requires that the intervention must be implemented within 3 hours of birth to ensure that the study intervention can be started: i.e. infants randomised to the intervention arm can be started on full milk feeds with minimal risk of having received IV fluids. Approaching mothers soon after delivery, a time that is emotionally fraught and potentially difficult, for written informed consent may not be appropriate as defined in Good Clinical Practice[25, 26] , therefore consent will be taken via two pathways (see Figure 1): antenatal written informed consent or postnatal oral assent followed by written informed consent. Written informed consent or oral assent (followed by written informed consent before inclusion of the participants' data) for each participant will be obtained prior to performing any trial related procedure. Women presenting in preterm labour may be consented via the antenatal or postnatal pathway, clinician discretion will be used to determine the most appropriate method.

Women who are approached to join the trial will be given the opportunity to ask questions throughout the process. Consent will be taken by the Principal Investigator or their delegate (e.g. co-investigator, research nurse) as documented on the Site Delegation Log. It remains the responsibility of the Principal Investigator to ensure informed consent is obtained appropriately and that those on the delegation log have been appropriately trained.

Antenatal pathway

Antenatal written informed consent pathway

Every effort will be made to approach women and families in the antenatal period, at or around the time of the neonatal antenatal counselling appointment. Women will be given study information, have an opportunity to discuss the study with a neonatologist or a member of the research team and will be asked to give full informed written consent antenatally wherever possible.

A Patient Information Sheet (PIS) will be provided to facilitate this process. The woman will be given sufficient time to read the PIS and to discuss their participation with others (e.g. family members, GP or other healthcare professionals outside of the site research team, if they wish). Investigators "or delegate(s)" will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to all women who are approached. Prior to taking consent, the Investigator "or delegate" should be satisfied that the woman has a full understanding of the trial. It will be clearly conveyed that participation is voluntary, not wishing to participate will in no way impact the care that they or their infant(s) receive and anyone who does consent may withdraw from the trial at any time.

If the woman does wish to participate with her infant(s) in the trial they will be asked to sign and date the Informed Consent Form (ICF). Both the Investigator "or delegate(s)" and the mother must sign and date the form at the time of the discussion.

For women enrolled via the antenatal pathway, once they have given birth, infant eligibility will be checked and infant(s) will be entered into the trial unless the mother expresses that she does not want her infant(s) to participate. This will be documented in the woman's and her infants' medical notes. If they choose for their infant to not participate at this point, the woman will not be randomised and no study-related procedures will take place, though reasons for declining randomisation will be documented, if given.

Antenatal oral assent pathway

For women who present in labour and may not have the opportunity to give written informed consent prior to birth but are able to given oral assent, we will ask for oral assent to indicate their willingness to participate. In such circumstances, the women will be randomised after the infant(s) is born and eligibility has been confirmed unless she withdraws consent. Training on the key points to include in the minimal information required to give during the discussion about the trial and oral assent will be included at the time of site initiation. Following this, at a time that is deemed acceptable, written informed consent will be obtained as in the postnatal pathway described below.

Postnatal (oral assent followed by written informed consent) pathway

For some women, receiving information and providing consent antenatally may not be possible, due to the rapid and unexpected nature of preterm birth. These women will be recruited via the postnatal pathway.

Some women may present in labour such that there is no opportunity or sufficient time to obtain antenatal consent. In such circumstances, as the time during preterm labour and after birth can be extremely stressful for the family, we will ask women presenting in these circumstances to give oral assent to indicate their willingness to participate after the delivery. Training on the key points to include in the minimal information required to give during the discussion about the trial and oral assent will be included at the time of site initiation. A short 'Patient Information Flyer' and short video animation will be available to support this discussion if required.

These oral assent pathways, features as part of guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) on "Obtaining Valid Consent to Participate in Perinatal Research where Consent is Time Critical[27]". This guidance states that in acute circumstances, it may not be appropriate to provide full study information at the time of a complication or there may not be time to fully discuss the study. For this situation, an oral consent pathway has been developed in collaboration with consumer groups, including the National Childbirth Trust. In line with this guidance, if a mother gives oral assent, the infant will be entered to enable the start of the trial intervention within 3 hours of birth. Following this, at a time that is deemed acceptable, written informed consent will be obtained. Women who lack the capacity to provide oral consent will not be enrolled in the trial. With the exception of the minimum data required for randomisation (see section 8.2.1), the mother and her infant(s)' data will only be entered into the trial after written consent is given. Should written informed consent not be obtained, data collected for randomisation will remain in the database unless the mother explicitly request this to be removed. Due to the stressful environment in which this consent is required, clinicians will use their discretion to determine an acceptable time point at which to obtain written consent. Mothers will receive a copy of the full PIS and will be given sufficient time to consider the information prior to being asked to provide written informed consent. Written informed consent should be obtained within 72 hours of oral assent unless there is an exceptional reason for the delay (such as an unwell mother) where the written informed consent should be obtained prior to the mother being discharged from hospital.

Where oral assent is obtained, a sticker, provided by Nottingham Clinical Trials Unit (NCTU), will be placed in the medical notes confirming that oral assent has been given and the time at which it was given. This will flag to the local team to ensure that written informed consent is obtained within 72 hours of this stated time.

Upon entering the maternal details into the trial randomisation database, the Investigator "or delegate(s)" will be prompted to first enter the mother's NHS number. Should the mother have been approached and enrolled via the antenatal pathway then the mother's enrolment information will be displayed. This will mitigate duplicate entries into the trial and the Investigator "or delegate(s)" can proceed to randomisation.

For infants recruited via either pathway, parents will have the opportunity to ask questions about the trial at any time. Any new information that may be relevant to the infant's continued participation will be provided. Where new information becomes available which may affect the mothers' decision to continue, participants will be given time to consider and if happy to continue

will be re-consented. Re-consent will be confirmed verbally and documented in the medical notes. The mother's right to withdraw from the trial will remain.

A copy of the ICF will be given to the woman, a copy will be filed in the woman's medical notes, and the original placed in the Investigator Site File (ISF). Once the woman is entered into the trial, the woman's unique trial identification number will be entered on the Informed Consent Form maintained in the ISF. In addition, a copy of the signed Informed Consent Form will be uploaded to the trial randomisation database in order for NCTU to review as a part of central monitoring. Details of the informed consent discussions will be recorded in the woman's medical notes. This will include date of discussion, the name of the trial, version number of the PIS given to participant and version number of ICF signed and date consent received. Participation in the trial will also be clearly documented in each eligible infant's medical notes.

If a woman declines to participate, this will be clearly documented in the woman's notes in order to mitigate the risk of the mother being approached repeatedly. Details of all mothers approached about the trial will be recorded on the Patient Screening/Enrolment Log.

The consent form will include consent to contact the mother via phone, letter, and/or email when the baby is 6 weeks corrected age (i.e. term gestation + 6 weeks old) for completion of the 6 week data collection. It will also include consent to obtain infants' data from the national neonatal research database (NNRD)which will be used to collect data outcomes including brain injury imaging results, retinopathy of prematurity screening, and chronic lung disease, where needed.

In addition, women will be asked to provide optional consent for longer-term follow-up in early childhood and later educational outcomes (separate funding application required). Two year follow up data will be collected via a questionnaire and, where needed from the routinely recorded 2 year follow-up data in the NNRD database.

6. Enrolment and Randomisation

6.1. Enrolment/Registration

All infants born between 30 weeks + 0 days and 32 weeks + 6 days in the participating institutions will be assessed for eligibility, where possible. Any mother for whom written consent or oral assent has been obtained and whose infant(s) meet the eligibility criteria, will be randomised and their infant(s) entered in to the trial within 3 hours of birth. In cases of multiple pregnancy, should not all infants be eligible, those who are eligible may still be entered into the trial. The care of non-eligible siblings will continue as per the preference of both the clinician and the mother.

For women who are enrolled into the trial but are not randomised, reasons for not randomising will be captured on the enrolment database.

Data will be collected for all participating infants until hospital discharge. For infants who are transferred to another hospital (known as the 'continuing care site'), a transfer pack will be sent with information on trial participation. The intervention will be continued and data collection completed by the continuing care site. The PI from the original recruiting site will be responsible for informing NCTU of the transfer and ensuring data collection is competed at the continuing care site. This will be facilitated by documentation about the trial that will be sent at the time of transfer identifying the continuing care site to the fact the infant is participating in the trial.

Mothers' contact details (postal address, email, and phone number) will be collected prior to discharge and stored securely within the trial database in order to send out questionnaires at 6 weeks corrected gestation age of the infant. To facilitate maintaining contact with mothers we will also ask for a secondary contact address, which will also be stored securely within the trial database. In addition, these contact details will be used to maintain ongoing contact with the mother for subsequent follow-up, provided (optional) consent has been obtained (separate funding application required).

As part of a separate funding application, funds will be sought to link to the participants' data in the NHS Digital records to check on the infants' wellbeing after discharge prior to making any further contact with the family. To maintain contact with families, birthday cards will be sent to infants on their birthdays. In addition, other study information, such as newsletters to update families on study progress, will also be sent in order to promote data collection and longer-term follow-up of infants.

6.2. Randomisation

The unit of randomisation is the mother. This will ensure that siblings from multiple pregnancies are assigned to the same group. We consulted mothers of multiple births via the Twins and Multiple Births Association (TAMBA), The Oxford Support for Sick Newborn and their Parents (SSNAP) and Bliss, the national charity for the newborn. The mothers told us they would not like to feed their infants differently unless there was a medical reason to do so. A similar approach of including all siblings in the same arm of the trial was used in the SIFT trial and was favourably received by the participating families[28].

Randomisation will be performed via a secure web-based system using a 1:1 ratio. The allocation will be concealed using a secure web-based system developed and maintained by the NCTU. Randomisation will use a minimisation algorithm, with a random element, to ensure balance on important prognostic factors: collaborating hospital; single or multiple birth; gestational age at birth, birthweight centile* and whether IV fluids were started prior to randomisation*. Randomisation will be undertaken by the Principal Investigator or a clinician or study team member, as per the site delegation log.

*data from the first eligible birth will be used for minimisation in the case of multiple pregnancies.

Randomisation within 3 hours of birth: Eligible infants will enter the trial via randomisation within 3 hours after birth. This is to ensure that the study intervention can be started: i.e. infants randomised to the intervention arm can be started on full milk feeds with minimal risk of having received IV fluids. In consultation with members of the Neonatal Nutrition Network, we have agreed on the 3 hours cut-off. This is in keeping with the time taken to complete delivery room stabilisation, transfer to neonatal unit, and to complete the admission process. It is also the maximum acceptable period that clinicians within the Neonatal Nutrition Network agreed they would wait before the need to provide some form of fluid to the infant. Randomisation within 3 hours should, therefore, prevent contamination between groups as the infants randomised to the full milk group will be able to receive full milk without need of IV fluids while waiting to be entered into the study.

Upon randomisation, a confirmation email will be automatically sent to the Investigator. Evidence of randomisation, including feeding allocation, will be printed from the web-based randomisation system and a copy filed in both the mother's and the infant's medical notes. Where acceptable, cot cards will be used to indicate an infant's feeding allocation and stickers will be placed on the front of the infant's medical notes.

6.3. Blinding and concealment

Blinding of both investigators and families is not possible due to the nature of the intervention. As a consequence, and to support the potentially subjective primary outcome, a secondary outcome will assess the time until the objective discharge criteria are met. This secondary outcome will be determined by outcome assessors blinded to treatment allocation, and is intended to remove any subjective bias that may be present in the clinician's decision to discharge an infant, due to their knowledge of the infant's treatment allocation.

In addition, a blinded endpoint review committee will be set up to examine the relevant Case Report Forms (CRFs) and, if necessary, the clinical notes of a sample of infants classified as having microbiologically confirmed or clinically suspected late-onset invasive infection or NEC. The BERC remit and instructions will be described in a separate 'BERC Charter' document prior to BERCs taking place.

Table 1: The blinding status of individuals involved in the trial

	Blinding status	**Comments**
Parents and infant	Not blinded	Not possible due to the nature of intervention. Parents will be informed which arm of the trial they have been randomised as soon as possible after randomisation
Principal investigator and other site staff	Not blinded	Not possible due to the nature of intervention. Following randomisation, an email will be sent to the PI and/or other site staff (as agreed locally) confirming allocation
Chief investigator	Blinded	The Chief Investigator will remain blinded to treatment allocation overall; however this is not possible for infants recruited at the University Hospitals of Derby and Burton NHS Trust, since she is responsible for their clinical care
Database programmer	Not blinded	The database programmer will be responsible for the management of the randomisation database and will also have access to unblinded datasets within the trial database.
Trial and data management staff	Not blinded	Trial and data management staff will have access to unblinded datasets within the trial database in order to undertake central monitoring.
Trial statistician	Blinded	The trial statistician will finalise the statistician analysis

		plan prior to treatment codes being revealed, i.e. prior to them becoming unblinded.
Independent statistician	Unblinded	A statistician independent to the trial team will be involved in the generation of closed reports for the Data Monitoring Committee (DMC) and will therefore be unblinded to trial intervention.
Members of the blinded endpoint review committee (BERC)	Blinded	Members of the BERC, will assess the CRFs and (if necessary) anonymised medical notes

7. Trial treatment / intervention

7.1. Treatment

Intervention: In the 'full milk' group, fluids will be started as milk at 60 ml/kg/day, increased as per the infant's fluid requirement in line with standard neonatal practice. The choice of feeding intervals will be determined by local policy and clinician's preference such as continuous feeding or 1, 2 or 3 hourly bolus feeding.

The intention will be to avoid using any IV fluids or parenteral nutrition unless feeds are not tolerated or IV fluids become indicated for other reasons (e.g. hypoglycaemia). They will continue other IV medication required for ongoing medical care (e.g. antibiotics).

Control: If mothers are randomised to the control arm, their baby will receive fluids as per standard practice at the site. This may include milk feeds, starting at a maximum of 30 ml/kg/day on day 1 of life with a minimum of 30ml/kg/day of supplementary IV fluids or parenteral nutrition.

7.2. Treatment Supply and Storage

7.2.1. Treatment Supplies

Wherever possible, expressed mother's breast milk will always be the first preference for infant milk feeds. Since randomisation is within 3 hours of birth, it is likely mother's breast milk will need to be supplemented with additional milk, i.e. either infant formula milk or donor breast milk. The decision as to the type of milk to be used will be made by the site and the mother and in accordance with the sites local policy for usual care.

7.2.2. Packaging and Labelling

Infant formula milk and donor breast milk will be used in accordance with the local site's usual policy. Supply of either type of milk is therefore outside of the trial and will be packaged and labelled in accordance with their usual local policy.

7.2.3. Storage of Treatment

Infant formula milk and donor breast milk will be stored in accordance with the local site's usual policy. There are no special requirements or considerations for the trial.

7.3. Dosing Schedule

Infants of mothers randomised to the full feeds arm will be started on 60 ml/kg/day of milk feeds. Feed increments will be as per the infant's fluid and nutritional requirements.

7.4. Treatment Interaction(s) or Contraindications

The FEED1 trial does not involve any Investigational Medicinal Product (IMP). All participating infants and mothers will receive standard care as per clinical needs and local guidelines. Medications given as part of normal clinical care may be administered without restriction at the discretion of the prescribing clinician. No medication or treatment are contraindicated due to participation in this trial. Participation in FEED1 does not preclude enrolment in other investigational studies, including clinical trials of IMPs. If needed, the CI of FEED1 and any potentially conflicting study can discuss and agree whether joint participation is possible.

7.5. Accountability Procedures

Daily feed and fluids logs from day 1 of life to the time of reaching full enteral milk feeds (at least 140 ml/kg/day for 3 consecutive days) will be used to record all fluid intake (including milk, IV fluids, parenteral nutrition, any other infusions) to monitor adherence with treatment. Adherence data will routinely be reviewed by the Trial Management Group.

- Adherence by those randomised to full milk feeds is defined as having received ≤24 hours IV fluids or parenteral nutrition from birth to achieving full milk feeds (defined as at least 140 ml/kg/day for three consecutive days).
- Adherence by those randomised to gradual milk feeds is defined as having received >24 hours IV fluids or parenteral nutrition from birth to achieving full milk feeds (defined as at least 140 ml/kg/day for three consecutive days).

7.6. Treatment Modification

Change from the allocated feeding regimen may be made at the discretion of the treating clinician if the infant appears unable to tolerate the allocated feeding regimen. All such cases will be recorded including the reason for deviating from the allocated feeding regimen.

8. Trial procedures and assessments

8.1. Summary of assessments

Figure 3 Summary of assessments by time point

	TRIAL PERIOD							
	Antenatal pathway	Postnatal pathway	Treatment period					Follow-up
TIMEPOINT	Before birth	After birth	Day_1	Day_2	Day_3	Etc.	Discharge	6 weeks corrected age
ENROLMENT:								
Eligibility screen	X	X						
Informed consent	X							
Oral assent[1]	X[1]	X[1]						
Randomisation			X					
Informed consent[2]	X[2]	X[2]						
Baseline data			X					
INTERVENTIONS:								
Full enteral feeds or Gradual feeds			X	X	X	X		
ASSESSMENTS:								
Daily feeding log			X	X	X	X		
Number of painful procedures			X	X	X	X		
Discharge criteria			X	X	X	X	X	
Late-onset Invasive Infection[3]			X[3]	X[3]	X[3]	X[3]		
Gut Signs[4]						X[4]		
DISCHARGE DATA:								
Growth (z scores - weight, length, and head circumference)							X	
FOLLOW-UP:								
Healthcare visits								X
Types and modes of feeding								X
Parental satisfaction (p-BESS)								X

[1] *Women who present in the late stages of labour or who have already given birth should be consented first via oral assent followed by later written informed consent*

[2] *Women who given oral assent trial should provide written consent within 72 hours of providing oral assent, where possible*

[3] *Each episode of microbiologically-confirmed or clinically-suspected late-onset invasive infection should be reported throughout the treatment period until hospital discharge*

[4] *To be reported if this infant has received at least 5 days of treatment for gut signs, if they are transferred with gut signs, or if they have died from gut signs*

8.2. Schedule of Assessments

The following assessments will be performed at each time point indicated:

8.2.1. <3 hours after infant(s) birth

- Check eligibility criteria
- Obtain oral assent (for women recruited via the postnatal pathway – see Section 5
- Collection of mother and baby demographic data
- Randomise mother into trial and inform family of allocation for their infant(s)

8.2.2. Post-randomisation

- For infants in the intervention arm, start full milk feeds at 60/ml/kg
- For infants in the control arm, start IV fluids and/or parenteral nutrition, as per local practice
- For women recruited via the postnatal pathway, obtain written informed consent as soon as it is deemed acceptable to do so, ideally within 72 hours of oral assent (see section 5 for consent procedures)

8.2.3. Daily data collection until infant receives 140ml/kg/day feeds, sustained for 3 days

- Daily feeding log
    - A record of the total volume of feeds, type of milk, methods of feeding, use of parenteral nutrition, record of any administered antibiotics or antivirals, record of any measured blood glucose levels, record of any feeds withheld for more than 4 hours.

8.2.4. Daily data collection until hospital discharge

- As per above and in addition;
- Number of intravenous cannula or central venous lines inserted
    - A daily record of whether central venous lines have been required (including umbilical and percutaneous or surgically inserted venous lines) and the number of days in situ.
    - A daily record of whether IV cannula has been required and the number of days in situ until full milk feeds (defined as at least 140 ml/kg/day for three consecutive days).
- Discharge criteria
    - A daily record of whether the infant has been weighed and an updated weight record.
    - A daily record of whether infant has been able to take at least one full suck feed at least 3 hourly intervals.
    - A daily record of whether infant has been off all additional temperature support for at least 24 hours.
- Late-onset Invasive Infection
    - A record of any diagnoses of microbiologically-confirmed (positive blood/CSF culture) or clinically-suspected late-onset sepsis (as per diagnostic criteria detailed in section 2.2).
- Gut signs
    - A record of any “gut signs” suggesting a diagnosis of necrotising enterocolitis (Bell’s stage 2 or 3).

8.2.5. Hospital discharge

- Z-scores for weight, and head circumference.
- Types and modes of feeding at discharge (including discharge on any nasogastric feeding).
- Need for home oxygen therapy.
- Results of retinopathy of prematurity screening, if performed as per routine screening criteria.

8.2.6. Survival

- Any instances of death during hospital stay will be reportable as a Serious Adverse Event (see section 9.4.2). The date and cause of death will be recorded in the appropriate section of the CRF.
- A search of hospital records will be carried out at 5 weeks corrected age, and any instances of death reported.
- For infants who have died, it is the investigators responsibility to provide the date and cause of death, where possible.

8.2.7. 6-weeks corrected gestational age (i.e. term gestation + 6 weeks age)

- Mother will be sent a postnatal questionnaire (either postal or online as per mothers' preference) to collect data on;
    - Types and modes of feeding at the time of questionnaire completion.
    - Any infant healthcare visits, including hospital visits.
    - Use of any other health care resources such as GP visits, antibiotics.
    - Parental satisfaction and wellbeing, using the p-BESS questionnaire.

Site staff will check hospital records for any record of infant death once the infant reaches 5 weeks corrected age. Any infant deaths will be reported to the NCTU within 24 hours of becoming aware of the event (see section 9.2) and will be recorded in the appropriate section of the CRF. Mothers of infants who have died will be sent an appropriately adjusted 6-week questionnaire and accompanying letter.

8.2.8. Additional Health Economic Data

- Number of delivery sets for parenteral nutrition/IV fluids during hospital stay.

8.3. Trial Procedures

8.3.1. Blinded endpoint review committee (BERC) standardisation

8.3.1.1. BERC standardisation of microbiologically confirmed LOS and NEC

Completed 'Gut Signs' forms (for reporting cases of NEC) and completed 'Late-Onset Invasive Infection' forms (for the reporting of cases of microbiologically confirmed or clinically suspected late-onset invasive infection) will be reviewed by appropriately qualified neonatal clinicians blinded to trial feeding allocation, where needed.

Any suspected inconsistencies in reporting will be queried with the relevant Principal Investigator.

8.3.2. Patient transfers

Data will be collected for all participating infants until hospital discharge. For infants who are transferred to another hospital (known as the 'continuing care site'), a transfer pack will be sent with information on trial participation. The intervention will be continued and data collection completed

by the continuing care site. The PI from the original recruiting site will be responsible for informing the trial co-ordinating site of the transfer and ensuring data collection is completed at the continuing care site. This will be facilitated by documentation about the trial that will be sent at the time of transfer identifying the continuing care site to the fact the infant is participating in the trial.

8.3.3. Withdrawal Procedure

If the mother chooses to withdraw her infant(s) from receiving the allocated intervention, she will be asked for her ongoing consent for us to complete data collection and/or follow-up.

If the mother chooses to withdraw her consent at any stage, she will be asked for the reason of withdrawal, though she can decline from giving a reason if she wishes. Any data collected up to the point of withdrawal of consent may still be used in trial analyses unless the mother has specified otherwise.

If the attending clinician withdraws the infant from treatment as they consider this to be in the best interest of the infant's health and well-being, we will continue to collect data unless the mother asks that the data collection is not to be completed.

Withdrawn infants will not be replaced. The sample size has allowed for up to 2% non-collection of primary outcome data (more details in section 13.1.1.

8.3.4. Sub study

We plan to embed a study within a trial (SWAT) into the FEED1 Study. The aim is to compare group-based training during the set-up of a trial versus visiting the site to conduct a Site Initiation Visit (SIV). At the start of a trial, SIVs are often conducted to deliver training to the Principal Investigator and their local research team to open the site to recruitment. The time required to visit all sites, particularly for large trials, can be burdensome during the resource intensive period of trial set-up. However, there is currently little evidence about the best way to deliver trial training to sites for sites to perform well. Evaluating methods of training was the number one priority identified by trialists at a workshop looking at recruitment and retention of participants to trials[29]. Two systematic reviews have been undertaken investigating training in clinical trials. The first showed there are a variety of different training methods described in trials[30] and the second concluded that more research is needed to determine what kind of training and support can improve recruitment[31]. A small study which retrospectively reviewed recruitment data and data completeness collected for two trials showed that, whilst face-to-face training (either at SIV or by a group training session) was associated with better recruitment than remote training (i.e. telephone or DVD), no difference was seen between the two types of face-to-face training[32].

The SWAT design is as follows:

Population:	All sites involved in the FEED1 Trial
Intervention:	Group-based training, by conducting collaborators' meetings.
Control:	SIV training. All sites randomised to the control group will be training on a per-site basis by the Trial Manager and a Neonatologist.
Outcomes:	Actual recruitment versus target recruitment Percentage of eligible individuals (women) who have consented Percentage of infants with query for primary outcome data Percentage of expected infants with complete data for primary outcome and important secondary outcomes of late-onset sepsis until hospital discharge (microbiologically-confirmed or clinically suspected) and necrotising entercolitis

Percentage of infants with at least one protocol violation
Associated costs (direct and in-direct) of delivering the training

The outcome measures are as per performance metrics defined by an NIHR funded project[33]. Outcome assessment will not take place before database lock.

Sites will be randomised to have their initial training delivered either during a visit by the research team to the site, or in a larger regional collaborators meeting; i.e. "group-based training". In order to be considered eligible for participation in the SWAT, sites must meet all of the following criteria:

1. Have completed the Site Selection Questionnaire
2. Been selected by the trial team following blinded review of the response to the Site Selection Questionnaire
3. Re-confirmed interest in participation upon approach

Sites will be randomised (1:1) to either (1) Group-based training or (2) SIV training. Randomisation will be balanced across each arm by the following variables, using data collected via the Site Selection Questionnaire:

1. Number of total births at 30^{+0} to 32^{+6} weeks gestation per month (continuous variable)
2. Level of neonatal care (categorical variable: level 1/level 2/level 3)

Sites randomised to the intervention arm of the SWAT will be invited to attend a group-based training session. Two sessions will be held during the set-up phase of the trial, each of which will involve approximately 10 sites. Additional supporting material may be developed and distributed to all sites as required.

The schedule for site initiation, based upon the SWAT and the internal pilot phase of the trial, is as follows:

	Number of sites involved in site initiation/training	
	Sites randomised to the intervention arm	Sites randomised to the control arm
Randomisation of first batch of sites	10 (i.e. first meeting)	10
Randomisation of second batch of sites	10 (i.e. second meeting)	10

We will use, as the outcome measures, a core set of performance metrics, developed in a study led by Nottingham Clinical Trials Unit and funded by NIHR[33].

Sites who are randomised to the intervention arm of the SWAT but who are unable to attend a group-based training session will be given a site specific SIV. Planning for group-based training sessions will begin as soon as is reasonably practicable, and multiple dates will be offered in order to

minimise non-attendance. The associated risk of an imbalance in arms is acknowledged and accepted.

9. Adverse Event Reporting

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK policy framework for Health and Social Care Research 2018 and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant, this should be documented in the source data with reference to the protocol.

9.1. Adverse Events

Adverse Events (AEs) are commonly encountered in infants receiving neonatal care and will be recorded in medical notes, as per usual practice. Adverse Reactions (ARs) are collected as outcomes for this trial and will not be reported on a separate AE CRF.

All routinely measured blood glucose levels (i.e. blood glucose measured as part of the participants' routine clinical care) will be recorded in the daily feed logs and data included in reports provided to the data monitoring committee. Management of hypoglycaemia will be as per routine practice and no changes in this management will occur due to participation in the trial.

9.2. Serious Adverse Events

Investigators will report AEs that meet the definition of an SAE, other than those listed in section 9.2.1. An SAE is defined as an AE that meets at least one of the below criteria:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity; and
- consists of a congenital anomaly or birth defect.

9.2.1. Events that do not require expedited (immediate) reporting

The following are regarded as expected SAEs for the purpose of trial and should not be reported on an SAE form.

Late-onset sepsis: A record of any diagnoses of microbiologically-confirmed (positive blood/CSF culture) or clinically-suspected late-onset sepsis (as per diagnostic criteria detailed in section 2.2). A 'Late onset invasive infection' form should be completed for each episode and entered onto the eCRF.

Necrotising enterocolitis (NEC): A record of any "gut signs" suggesting a diagnosis of necrotising enterocolitis (Bell's stage 2 or 3). A 'gut-signs' form should be completed for each episode and entered onto the eCRF.

Known complication(s) of prematurity: any event that is deemed by the investigator to be a known complication of prematurity should not be reported but should be recorded in the infant's medical notes, as per usual practice.

9.3. Reporting period

All AEs should be recorded in the medical notes from the commencement of treatment allocation until the infant is discharged from hospital. For infants transferred to another hospital during their participation in the trial, the randomising hospital retains all responsibility for the collection of data from the receiving hospital and the ongoing reporting of AEs.

9.4. Reporting Procedure – At Site

9.4.1. Adverse Events

AEs are commonly encountered in participants receiving neonatal care due to prematurity and will be recorded in the infant's medical notes. Selected AEs are outcomes for the trial and will be recorded in the CRF.

9.4.2. Serious Adverse Events

Any AE that meets the criteria of an SAE, with the exception of those outlined in section 9.2.1, should be reported on an SAE form. When completing the form, the Investigator will be asked to define the causality and the relatedness to trial interventions.

The Investigator (or delegate) must complete, date and sign an SAE Form. The form should arrive at NCTU by email or fax (as below) as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, email the SAE Form to:	nctu-sae@nottingham.ac.uk
Or fax the SAE Form to:	0115 74 84092

On receipt, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, the site will contact the NCTU. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the Site File.

For SAE Forms completed by someone other than the local Principal Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to NCTU and a copy kept in the Site File. Investigators should also report SAEs to their own Trust in accordance with local practice.

9.4.3. Provision of follow-up information

Only SAEs that are deemed to be related to trial interventions will be followed-up to resolution.

9.5. Reporting Procedure – NCTU

On receipt, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE form in the TMF.

On receipt of an SAE Form seriousness and causality will be determined independently by the Chief Investigator or their delegate (a neonatologist co-applicant) responsible for determining causality assessments. The Chief Investigator's delegate will review all SAEs reported by the Chief Investigator's host site. An SAE judged by the Investigator or Chief Investigator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Chief Investigator

will also assess all related SAEs for expectedness. If the serious event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.6. Reporting to the Research Ethics Committee

9.6.1. Unexpected and Related Serious Adverse Events

NCTU will report all events categorised as Unexpected and Related SAEs to the REC within 15 days.

9.6.2. Adverse Events

The REC will be notified immediately if a significant safety issue is identified during the course of the trial.

9.7. Investigators

Details of all Unexpected and Related SAEs and any other safety issues which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Site File.

9.8. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review neonatal outcome data at regular intervals throughout the trial, in addition to reported SAEs.

10. Data Handling and Record Keeping

10.1. CRF Completion

Data will be reported using an electronic Case Report Form (eCRF). Reported data will be consistent with the source data (see section 10.2) and any discrepancies will be explained. Staff delegated to complete the eCRF will be trained to adhere to ICH-GCP guidelines and trial-specific guidance on the completion of the eCRF, in particular:

- Date format and partial dates
- Time format and unknown times
- Rounding conventions
- Trial-specific interpretation of data fields
- Entry requirements for concomitant medications (generic or brand names)
- Which forms to complete and when
- What to do in certain scenarios, for example if a participant withdraws from the trial
- Missing/incomplete data
- Repeat laboratory tests
- Protocol or GCP non-compliances

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the eCRF has been completed correctly and that the data are accurate, as evidenced by their signature on the eCRF. It is the responsibility of the site's Principal Investigator to ensure there are site staff in place to complete data entry into the eCRF. To assist with data completion, sites will be provided with paper CRF workbooks, data will then be entered onto the eCRF by the investigator "or delegate(s)". Where data is collected first onto a CRF workbook, it should be entered into the eCRF within 7 days.

10.2. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained. Source data is kept as part of the

woman's and infant's medical notes generated and maintained at site. Each site will record the location of source data at their site using a source data location log. Data that is not routinely collected elsewhere may be entered directly onto the paper CRF workbooks or the eCRF; in such instances the CRF workbook or eCRF will act as source data, this will be clearly defined in the source data location log.

For this trial, source data refers to, though is not limited to, the woman's medical notes, infants' medical notes, women's & infants' local electronic case records (including but not limited to Badger.net), blood/CSF culture results, data recorded directly onto the CRF (as per the source data location log), data entered into the national neonatal research database, and postnatal questionnaires.

10.3. Data Management

All trial data will be entered on a trial specific database through the eCRF with participants identified only by their unique trial number and initials. The database will be developed and maintained by NCTU. Access to the database will be restricted and secure. Any missing or ambiguous data will be queried with the site via the eCRF, sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised.

Data should be entered directly into the eCRF where possible. CRF workbooks will be provided to sites to assist with the collection of data, any completed CRF workbooks should be stored in a secure location separate from any identifiable information to prevent direct data linkage. For infants with missing data (for example if an infant has been transferred to another hospital and data has not been obtained from the continuing care site), data will be obtained through NNRD and/or Badger.net where possible.

For the follow-up of participants at 6 weeks corrected gestational age, identifiable information about participants (i.e. contact details) will be entered by the sites into the online randomisation system. This information will be held in a separate database to the trial anonymised data. Access to this information will be restricted to those involved in the follow-up phase, as authorised by the CI. A secure link to an online questionnaire will be sent to parents at 6 weeks corrected gestational age. For parents who don't have internet access or prefer to complete a paper copy, a paper version of the questionnaire will be sent to their home address by NCTU, with a pre-paid return envelope.

Questionnaires returned to NCTU will be entered by qualified staff at NCTU. Data obtained from these patient reported outcomes will not be subject to data queries. The trial management team will follow-up (via telephone, text message, post or email) outstanding questionnaires to achieve maximum adherence. Data may be collected directly via these methods if required.

10.4. Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 5 years after the end of trial as defined in section 12. No documents will be destroyed without prior approval from the Sponsor.

11. Quality control and quality assurance

11.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a signed and dated current CV, and a copy of their current GCP certificate, to the NCTU. All members of the site research team will also be required to sign a site delegation log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed aspects of GCP training appropriate for the trial. The type of site initiation will depend upon randomised allocation to the SWAT, as per section 8.3.1. 20 sites will receive a site initiation visit and 20 sites will receive initiation training as part of a group meeting. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. NCTU must be informed immediately of any change to the site research team.

11.2. Monitoring

11.2.1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any on-site monitoring activities carried out by NCTU will be detailed in a monitoring report, a copy of which will be provided to the Sponsor. Any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, lower or higher than expected SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the FEED1 trial staff access to source documents as requested.

11.2.2. Central Monitoring

NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed Informed Consent Forms for in-house review for all participants. This will be detailed in the monitoring plan and the Participant Information Sheet.

Further central monitoring activities will be carried out in accordance with the monitoring plan.

11.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

11.4. Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the NCTU is investigating whether or not a serious breach has occurred sites are also requested to cooperate with NCTU in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the sponsor, Trial Steering Committee, Data Monitoring Committee and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC.

12. End of Trial Definition

The end of trial will be 6 months after the last data capture. NCTU will notify the REC the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

If women provided their consent to receive a copy of the trial results, a newsletter will be sent to them alongside their publication in a scientific journal. Results will be shared with sites at a results meeting once analyses are completed.

13. Statistical Considerations

13.1.1. Sample size calculation

Data from audits and previous studies suggest that the distribution of length of hospital stay in this population is approximately normal, with a mean length of hospital stay between 20 and 40 days and standard deviation between 9 and 16 days. Our parental representative feels that from a family perspective reducing length of hospital stay by even a couple of days would make a huge difference, despite the long overall length of stay for these infants. Families would be reunited sooner and the financial stress of preterm birth on families would be reduced substantially. In addition, reduction in length of hospital stay by 2 days for this large group of infants would equate to £5.6 million annual savings for the NHS in England and Wales resulting in over 12,000 days of increased neonatal cot capacity. This would lead to a significant positive impact on efficiency, improved quality of care, and cot space pressure in neonatal services across the UK.

Using a standard deviation of 13, the estimated sample size to detect a between group difference in means of 2 days with 90% power is 1778 infants for a trial without clustering. Based on data from the SIFT trial, we expect that 15% and 1.4% of pregnancies will be twin and triplets respectively, and that the intracluster correlation coefficient for length of hospital stay for infants from the same pregnancy to be 0.82, requiring a 15% inflation of sample size. We will also allow for up to 2% non-collection of the primary outcome due to death, non-consent for use of data after oral assent and infants remaining in hospital at the end of data collection. A sample size of 2088 infants is therefore needed (1778*1.15/0.98), requiring recruitment of 1770 women.
A trial of this size will also have 80% power to detect differences of 2.2 days if the standard deviation is 16 days.

13.2. Analysis of Outcome Measures

The analysis and reporting of the trial will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted according to randomised allocation with due emphasis on confidence intervals for between-arm comparisons. A full statistical analysis plan will be developed prior to completion of data collection, and agreed with the Trial Steering Committee before data are unblinded.

Descriptive statistics of demographic and clinical measures will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be made. Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages.

The primary comparative analysis will employ linear mixed modelling to compare the mean length of hospital stay between groups, adjusting for minimisation variables and accounting for the correlation between outcomes for infants born from a multiple pregnancy. The estimated between group effect will be presented using the difference in means, with a 95% confidence interval.

Secondary outcomes will be analysed using appropriate multilevel regression models depending on the type of outcome variable, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. The between group effect will be reported using an appropriate effect estimate along with a corresponding 95% confidence interval. The analyses of secondary outcomes will be considered supportive to the primary and estimates and p-values, where presented, should be interpreted in this light.

It is anticipated there will be very little missing primary outcome data, therefore the primary approach to between-group comparative analyses will be by modified intention-to-treat (i.e. including all participants who have been randomised and without imputation of missing outcome data). In particular, the primary analysis will exclude deaths, but sensitivity analyses using imputation will be used to check that this does not influence the findings.

The primary analysis will be repeated additionally adjusting for any variables with marked imbalance at baseline to check that this does not influence the findings. The effect of adherence with the allocated feeding strategy will be investigated using instrumental variable regression methods.

Time until discharge and time until objective discharge criteria are met will be compared between groups using multilevel time-to-event models, adjusting for minimisation variables and accounting for the correlation between outcomes for infants born from a multiple pregnancy.

13.2.1. Planned Interim Analysis

13.2.1.1. Stop-Go criteria for the internal pilot phase

An internal pilot phase has been built-in to the trial and Stop-Go criteria (Table 2) will be assessed after the first 9 months of recruitment.

Table 2: Stop-Go criteria for the internal pilot phase

	Progression Criteria		
	Green (go)	Amber (pause)	Red (stop)
Recruitment rate relative to overall target after 9 months*	>145	112-145	<112
Sites trained and open to recruitment after 9 months*	>26	22-25	<22
Adherence; randomised to full milk feeds and receives <24 hours IV fluids	≥ 85%	75-85%	<75%
Adherence; randomised to IV fluids and receives >24 hours IV fluids	≥ 85%	75-85%	<75%
Action to be taken based on type and number of criteria met	Proceed with protocol unchanged if ALL criteria are met	Address concerns/adapt protocol	Project feasibility doubtful consider ending trial if TWO/MORE criteria are met

*after 9 months of recruitment. Recruitment targets are based on number of women randomised.

13.2.2. Planned Final Analyses

Final analyses will be undertaken once the database has been locked, as per the end of trial definition in section 12.

13.2.3. Planned Sub Group Analyses

Appropriate interaction terms will be included in the primary regression analyses in order to conduct subgroup analyses according to the following subgroups:

- gestation at birth
- birth weight centile

Between-group treatment effects will be provided for each subgroup, but interpretation of any subgroup effects will be based on the treatment-subgroup interaction and 95% confidence interval, estimated by fitting an appropriate interaction term in the regression models. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses will be regarded as exploratory.

13.2.4. Additional exploratory analyses

An additional exploratory analysis will be carried out to compare the primary outcome and key secondary outcomes between infants who only received donor human milk and those who only received preterm formula milk to supplement mother's breast milk.

14. Health economic analysis

Economic analysis will be conducted alongside the clinical trial and adopt an NHS and personal social services perspective. Resource use data will be collected prospectively: duration of infant stay in hospital differentiated by level of care, duration and amount of parental feeding before being discharged home, formula milk, IV cannulas, antibiotic usage, any additional procedures associated with adverse events and readmissions to hospital. Unit costs will be obtained from routine sources such as NHS reference costs[34] and Unit Costs of Health and Social Care[35], will be attached to each resource item to generate an overall cost per patient. An incremental approach will be adopted with a focus on the resource use and outcome differences between the two trial groups. The main cost-effectiveness analysis will be based on the cost per reduction in days in care (intensive, high dependency and special care). Other intermediate outcomes will include cost per NEC or sepsis avoided. As cost data are usually skewed, we will use non-parametric bootstrapping[36] to produce 95% confidence intervals around the mean cost estimate. The results will be presented using cost-effectiveness acceptability curves. These curves plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness. We will use sensitivity analyses to explore the robustness of these results, and to consider the broader issue of the generalisability of the results.

A longer-term projection of costs and benefits will be estimated through decision analytic modelling that will allow extrapolation beyond the trial data (beyond 6 weeks post-partum). We will use various time horizons (most likely 1 and 5 years) to see the impact of the most optimal method of feeding preterm infants on the number of serious morbidities averted such as sepsis or NEC. The longer-term cost-effectiveness analysis will estimate the cost per case of serious infant morbidity averted. Information to populate the model will come from published literature supplemented if necessary, by expert opinion.

15. Trial Organisational Structure

15.1. Sponsor

This trial is sponsored by the University Hospitals of Derby and Burton NHS Foundation Trust.

15.2. Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU) based at the University of Nottingham.

15.3. Trial Management Group

The TMG will consist of the CI, Professor of Pediatrics, Professor of Clinical Trials and Medical Statistics, Assistant Professor of Clinical trials, Trial Statistician, Trial Manager, Senior Trial Manager and Data Coordinator. They are responsible for the day-to-day management of the trial and will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of data collected in the trial. Other relevant members of the trial team will be invited to TMG meetings as required.

15.4. Trial Steering Committee

The TSC will provide independent oversight of the trial and will meet at least annually or more often as required, either face-to-face or by teleconference. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC), and in accordance with the TSC Charter, and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

After 9 months of recruitment, the TSC will be presented with the data required to assess the Stop-Go criteria for the internal pilot phase of the trial (see section 13.3.1.1). The TSC and Data Monitoring Committee (DMC) will review the Stop-Go data and advise whether the trial should continue, outlining any concerns/required adaptations.

15.5. Data Monitoring Committee

Reports will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet initially during the trial set-up period to agree the content of the DMC charter. They will then meet 9 months after recruitment of the first infant (to coincide with the assessment of the Stop-Go criteria – see section 13.2.1.1) and annually after unless there is a specific reason.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee (TSC) who will convey the findings of the DMC to the funders, and/or Sponsor as applicable.

After 9 months of recruitment, the DMC will be presented with the data required to assess the Stop-Go criteria for the internal pilot phase of the trial (see section 13.3.1.1). The DMC and TSC will review the Stop-Go data and advise whether the trial should continue, outlining any concerns/required adaptations.

15.6. Finance

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (funding award number: 17/94/31).

Payments to co-investigators and recruiting sites will be covered in separate contractual agreements, located in the Trial Master File, and are not detailed in this protocol.

16. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, , the applicable UK Statutory Instruments, which include the Data Protection Act 2018) and the ICH Guideline for Good Clinical Practice E6 (R2) .

Other ongoing studies: There is a risk that women may be approached for participation who are already enrolled in a trial elsewhere. This is unlikely to be a problem in this group of infants as they are studied much less frequently in comparison to very preterm infants. If it is an issue, all trial centres are experienced in recruiting infants to multiple trials. Our experience (and that reported in the literature) is that this can be conducted appropriately and sensitively, and that parents in this situation are capable of making an informed decision about whether they wish to participate[32]. Where necessary the Chief Investigator will discuss and agree whether co-enrolment is acceptable with other study investigators.

Consent process: Ethical considerations for the consent process are outlined in Section 5.

Promotion of breast milk feeding: The study intervention involves feeding full volumes of milk from day 1 of life. As in standard practice and regardless of treatment allocation, the first choice will always be mother's own milk unless there are medical contraindication to feeding mother's milk or the mother chooses to formula feed. Infants randomised to both groups will be fed via a gastric feeding tube as per standard practice for infants born at 30^{+0}- to 32^{+6} weeks gestation. Mothers in both groups will be given information about the benefits of breast milk for preterm infants and fully supported to express milk and breast feed. This will be highlighted in site training. However, the trial intervention involves infants receiving full volumes of milk feeds from day 1. It is likely, in some cases, in the first few days, mother's own milk will not be sufficient in volume. Infants in the gradual milk group will receive supplemental IV fluids. For the full milk group, instead of the usual IV fluids, supplementation will be by donor breast milk, where available subject to mother's agreement. Substitutes for human milk (formulae) will be used if mother's milk is insufficient in volume and donor breast milk is not used at that study site or is unacceptable to the woman. Donor breast milk or formula milk will only be used as replacement for IV fluids or parenteral nutrition and not to replace mother's own milk. No milk other than mother's own breast milk be used if there is a sufficient volume of mother's milk available and there are no contraindications to feeding mother's milk. When a mother is producing the required volume, all substitutes will be stopped. All mothers will be advised and supported to continue exclusive own breast milk feeding when sufficient milk is available. The aim of the trial is to assess the potential benefits of milk feeding over intravenous nutrition. All study leaflets, posters and other materials used for purposes such as communication, recruitment, and dissemination of results will emphasise the goal of achieving full feeds with

mother's own milk with use of substitutes limited to supplemental volumes over a short period of time while waiting for mother's milk production to increase. Important aims of this study are to normalise the care of infants born at 30^{+0}-32^{+6} week's gestation by promotion of milk feeding and encouraging families to be more involved in their infant's care. This, we expect, will encourage mothers to express breast milk sooner and promote breast milk feeding.

All substitutes will be bought at market price from usual suppliers. There will be no involvement, financial or otherwise, of any formula milk manufacturer or related organisation in the study. To check the effect of this intervention on breast-feeding rates, we have included 'Types and modes of feeding' at discharge and 6 weeks as secondary outcomes. We plan to apply to other funding calls to qualitatively explore the socio-cultural and anthropological impact of the intervention on women's perception of neonatal care and breast milk feeding.

17. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using only their unique trial identification number and initials on the Case Report Form and in correspondence between NCTU and the participating site. Participants will give their explicit consent for the movement of their consent form, giving permission for NCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. NNRD). Representatives of NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

18. Insurance and Indemnity

The University Hospitals of Derby and Burton NHS Foundation Trust will act as sponsor for the trial. Delegated responsibilities will be assigned to the Chief Investigator, NHS Trusts taking part and NCTU. Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The University Hospitals of Derby and Burton NHS Foundation Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. Publication Policy

During the period of the trial, press releases may be issued from NCTU. No party will be entitled to submit any publicity material without prior approval from NCTU.

Plans for publication will be outlined in a separate publication plan, which will include details of authorship. Results of this trial will be submitted for publication in a peer reviewed journal(s). The manuscript(s) will be prepared by the Chief Investigator and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigators and members of the Trial Management Group as required. Manuscripts must be submitted to the Chief Investigator and Trial Manager in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University Hospitals of Derby and Burton NHS Foundation Trust.

Trial publications and conference abstracts will be submitted to the National Institute for Health Research (NIHR) for approval prior to submission to the event organisers or the editors. All publications will acknowledge the support of the NIHR in funding this trial. Neutral or negative results will not constitute a reasonable justification to delay publication. A lay summary of the results will be sent to all parents at the end of the trial.

20. Reference List

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