# A randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age) (FEED1)

# Statistical Analysis Plan

## Final Version 2.0

## (03 February 2025)

Based on Protocol version 2.3 (dated 13 April 2023)

Trial registration: ISRCTN89654042

| The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents | | | | |
|---|---|---|---|---|
| **Name** | **Job title** | **Trial Role** | **Signature** | **Date** |
| Yuanfei Su | Medical Statistician | Trial Statistician (Author) | | 03Feb2025 |
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| Christopher Partlett | Assistant Professor of Medical Statistics and Clinical Trials | Trial Statistician (Author) | | Feb 3, 2025 |
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| | | | | |
| Ben Stenson | Consultant Neonatologist | Chair of the Trial Steering Committee | | Feb 6, 2025 |

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## Abbreviations

| Abbreviation | Description |
|---|---|
| DMC | Data Monitoring Committee |
| SAP | Statistical Analysis Plan |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| P-BESS | The Preterm Birth Experience and Satisfaction Scale |
| CI | Confidence Interval |
| PARCA-R | Parent Report of Children's Abilities-Revised |

## Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol which after discussion with the TMG are not considered to require a protocol amendment.

| Protocol version and section | Protocol text | SAP version and section | SAP text | Justification |
|---|---|---|---|---|
| Version 2.3 section 13.2 | 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. | Version 1.3 | | After a blinded review, it was concluded that a sensitivity analysis would not add additional value to the analysis of the primary outcome, given the high completeness of the primary outcome data. |

## Amendments to versions

| Version | Date | Change/comment | Statistician |
|---|---|---|---|
| **1.0** | **01-Oct-2019** | **First version approved.** | **Christopher Partlett** |
| **1.1** | **17-Dec-2020** | **Minor changes to wording of outcomes following protocol amendment. Corrected description of BERC review process for LOII and NEC. Re-classifying CACE analysis as a secondary analysis.**<br><br>**Clarified alternative analysis methods for the primary analysis if model assumptions are not valid.**<br><br>**Corrected description of the analysis for the P-BESS and clarified that the unit of analysis for this outcome is the mother.** | **Christopher Partlett** |
| **1.2** | **26-Jan-2022** | **Added two years follow-up outcomes following variation to contract and protocol amendment.** | **Yuanfei Su** |
| **2.0** | **03-Feb-2025** | **Added questionnaire to collect reasons for non-adherence to allocated treatment.**<br><br>**Removed CACE analysis from secondary analysis following agreement with the TMG that only the estimand based on treatment policy strategy would be relevant, hence ITT as the sole analysis population for primary outcome.** | **Yuanfei Su** |

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|---|---|---|---|
| | | **Updated the derivation of brain injury.**<br><br>**Added details on Estimand for primary outcome including how to account for intercurrent events.**<br><br>**Removed sensitivity analysis for missing data due to deaths prior to discharge for primary outcome.** | |

## 1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the NIHR HTA funded FEED1 trial.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan.

This analysis plan will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This should be documented in a file note.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis.

Health economic and qualitative analysis plans are beyond the scope of this document.

## 2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

| | |
|---|---|
| Title | A randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age) |
| Acronym | FEED1 |
| Short title | Feeds Exclusively Enteral from Day One |
| Chief Investigator | Shalini Ojha |
| Objectives | 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. |
| Trial Configuration | Multi-centre, open, parallel, randomised controlled, superiority trial |
| Setting | Level 3 - Neonatal Intensive Care Unit<br>Level 2 - Local Neonatal Unit |
| Sample size | 2088 infants requiring recruitment of 1770 women. |
| Eligibility criteria | **Inclusion Criteria**<br>1. Infant born at 30 weeks + 0 days to 32 weeks + 6 days gestation, inclusive<br>2. Infant <3 hours (180 minutes) old (since recorded time of birth)<br><br>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.<br><br>**Exclusion Criteria**<br>1. Infant with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe<br>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<br>3. Mother has participated in the trial during a previous pregnancy |
| Description of interventions | **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.<br><br>**Control:** Parenteral nutrition/intravenous fluids with gradual milk feeding as per usual local practice. |
| Duration of trial | The trial will recruit over 60 months:<br>1st October 2019 to 30th September 2024. |
| Randomisation and blinding | 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.<br><br>*data from the first eligible birth will be used for minimisation in the case of multiple pregnancies. |
| Outcome measures | **Primary outcome**: Length of hospital stay<br>**Secondary outcomes:**<br>− Discharge<br>• Survival to hospital discharge<br>• Incidence of microbiologically-confirmed (positive blood/cerebrospinal fluid [CSF] culture) or clinically suspected (defined by diagnostic criteria [1]) late-onset sepsis until hospital discharge<br>• Necrotising enterocolitis (Bell's stage 2 or 3 [2]) until hospital discharge<br>• Time taken to maintain full milk feeding (defined as at least 140 ml/kg/d for three consecutive days)<br>• Time to regain birth weight<br>• Growth z-scores corrected for gestational age at hospital discharge (as per UK-NICM growth charts):<br>− weight<br>− length<br>− head circumference<br>• Any breast-feeding at hospital discharge<br>• Exclusive breast-feeding at hospital discharge<br>• Mother's breast milk fed at hospital discharge<br>• Number of days of peripheral cannula until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved<br>• Number of IV cannulae inserted until full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) achieved<br>• Number of days of parenteral nutrition, until hospital discharge<br>• Number of central venous lines inserted (including umbilical and percutaneous or surgically inserted venous lines) until hospital discharge<br>• Number of central line days until hospital discharge<br>• Retinopathy of prematurity (ROP) until discharge<br>• Chronic lung disease (CLD) until discharge<br>• Brain injury on imaging until discharge<br>• Time until objective discharge criteria are met (see section 2.2.1)<br>• Length of stay in<br>i. intensive care,<br>ii. high dependency care,<br>iii. special care,<br>iv. translational care<br>− Six weeks corrected age |

| | |
|---|---|
| | • Survival to 6 weeks corrected gestational age (i.e. term gestation + 6 weeks)<br>• Hospital visits (including day care and overnight admissions) up to 6 weeks of corrected age<br>• Breast-feeding at 6 weeks of corrected age<br>• Mother's breast milk fed at 6 weeks of corrected age<br>• Parental satisfaction and wellbeing at 6 weeks of corrected age, using the Preterm Birth Experience and Satisfaction Scale (p-BESS) questionnaire [3].<br>– Two years corrected age<br>• Survival to 2 years corrected age without moderate to severe neurodevelopmental impairment<br>• Survival to 2 years corrected age<br>• Moderate to severe cognitive impairment<br>• Moderate to severe language impairment<br>• Moderate to severe gross motor impairment<br>• Moderate to severe visual impairment<br>• Moderate to severe hearing impairment |

## 2.1. Sample size and justification

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.

*Power of the study to detect meaningful difference in neurodevelopmental outcomes at 24 months corrected gestational age*

Assuming 85% of infants in the control group survive without moderate or severe disability at 24 months corrected age (based on SIFT infants born at 30+0 to 31+6 weeks gestation), accounting for clustering within multiple births (ICC of 0.06), this sample size will allow 90% power to detect an absolute increase of 5.4% in survival without moderate or severe disability at 24 months corrected age, based on a two-sided 5% significance level and allowing for 20% loss to follow up.

## 2.2. Blinding and breaking of blind

Blinding of both local investigators and families is not possible due to the nature of the intervention.

The trial statistician will remain blinded prior to treatment codes being revealed (for the final analysis). 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.

A blinded endpoint review committee (BERC) 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. A BERC will also be set up to review clinical information for infants who are lost follow-up at 24 months corrected gestation age and infants whose outcomes cannot be confirmed through their 2-year follow-up questionnaires in order to classify the neurodevelopmental outcomes where possible.

## 2.3. Trial committees

A trial management group (TMG), trial steering committee (TSC) and data monitoring committee (DMC) will be assembled to oversee the trial. The general purpose, responsibilities and structure of the committees are described in the protocol. Further details of the roles and responsibilities of the TSC and DMC can be found in their charters agreed prior to the start of recruitment to the trial.

## 2.4. Outcome measures

The outcome measures and their derivations are summarised in *Table 1*.

*Table 1: Summary of outcome measures*

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| **Primary outcome** | | | |
| Length of hospital stay | Derived from date of discharge (Hospital Discharge) and date of randomisation. | Date of discharge home minus date of randomisation. | Difference in means (95% CI)<br>p-value |
| **Secondary outcomes at discharge** | | | |
| Survival to hospital discharge | Derived from date of death (Death form) and date of discharge (Hospital Discharge). | Binary indicator on presence of a date of discharge (Y/N).<br><br>Confirmed no if a date of death is present and there is no date of discharge. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Microbiologically-confirmed or clinically suspected late-onset sepsis until hospital discharge | Derived from Late-onset invasive infection (LOII) forms and blinded endpoint review of LOII forms. | Each LOII form will be assessed and signed-off by the site PI. For cases where the PI is in agreement with the original classification of microbiologically-confirmed or clinically suspected late-onset sepsis no blinded endpoint review is required.<br><br>Cases where the PI assessment is inconsistent with the original assessment will be reviewed by the blinded endpoint review committee to make a final determination. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | Infants discharged without a LOII form will be considered to have not met the outcome. | |
| Necrotising enterocolitis (Bell's stage 2 or 3) until hospital discharge | Derived from Gut-signs (GS) forms and blinded endpoint review of GS forms. | Each GS form will be assessed and signed-off by the site PI. For cases where the PI is in agreement with the original classification of NEC no blinded endpoint review is required.<br><br>Cases where the PI assessment is inconsistent with the original assessment will be reviewed by the blinded endpoint review committee to make a final determination.<br><br>Infants discharged without a GS form will be considered to have not met the outcome. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Time taken to maintain full milk feeding (defined as at least 140 ml/kg/d for three consecutive days) | Derived from the date the infant achieved three consecutive days of at least 140 ml/kg/day (Daily feed log) and date of randomisation. | Date achieved full milk feeding minus date of randomisation. | Hazard Ratio (95% CI) |
| Time to regain birth weight | Derived from date regained birth weight (Hospital Discharge) and date of randomisation. | Date regained birthweight minus date of randomisation. | Hazard Ratio (95% CI) |
| Growth z-scores corrected for gestational age at hospital discharge (as per UK-NICM growth charts) | Derived from growth scores at discharge (Hospital Discharge), expected date of delivery (Enrolment Mother) and infant sex (Infant Eligibility) using UK-NICM growth charts. | Derived using Stata package zanthro with UK-WHO growth chart [4]. | Difference in means (95% CI) |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| Any breast-feeding at hospital discharge (Yes/No) | Derived from modes of feeding (Hospital Discharge). | Yes: Any infant for whom breastfeeding has been selected meets the outcome.<br><br>No: if breastfeeding has not been selected, and at least one other mode of feeding has been selected. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Exclusive breast-feeding at hospital discharge(Yes/No) | Derived from modes of feeding (Hospital Discharge). | Yes: Any infant for whom **only** breastfeeding has been selected as the mode of feeding.<br><br>No: if breastfeeding has not been selected, or at least one other mode of feeding has been selected. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Mother's breast milk fed at hospital discharge (Yes/No) | Derived from types of feeding (Hospital Discharge). | Yes: Any infant for whom mother's breast milk has been selected (either expressed or on demand) meets the outcome.<br><br>No: if mother's breast milk has not been selected, and at least one other type of feeding has been selected. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Number of days of peripheral cannula until full milk feeding | Derived from cannula information (Daily Feed Log) | The number of days "Is there an IV cannula in today?" is ticked until full milk feeding achieved. | Descriptive |
| Number of IV cannulae inserted until full milk feeding | Derived from cannula information (Daily Feed Log) | Sum of "How many new cannulas inserted today?" until full milk feeding is achieved. | Descriptive |
| Number of days of parenteral nutrition, until hospital discharge | Collected on Hospital discharge form. | | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| Number of central venous lines inserted (including umbilical and percutaneous or surgically inserted venous lines) until hospital discharge | Collected on Hospital discharge form. | | Descriptive |
| Number of central line days until hospital discharge | Collected on Hospital discharge form. | | Descriptive |
| Time until objective discharge criteria are met | Derived from date objective discharge are met (Hospital Discharge) and date of randomisation. | The date objective discharge criteria are met minus date of randomisation. If any of the discharge criteria have not been met by discharge then the observation is censored at the time of discharge. | Hazard Ratio (95% CI) |
| Length of stay in<br>(i) intensive care,<br>(ii) high dependency care,<br>(iii) special care,<br>(iv) translational care | Collected on Hospital discharge form. | | Descriptive |
| Retinopathy of prematurity (ROP) until discharge | Collected on Hospital discharge form. | | Descriptive |
| Chronic lung disease (CLD) until discharge | Collected on Hospital discharge form ( Bronchopulmonary dysplasia; mechanical ventilator support via endotracheal tube or nasal CPAP at 36 weeks PMA; or supplemental oxygen at 36 weeks PMA). | | Descriptive |
| Brain injury on imaging until discharge | Derived from intracranial abnormality, periventricular leukomalacia, and shunt for hydrocephalus that are collected on Hospital discharged form. | An infant will be classified as having brain injury on imaging if any of intracranial abnormality, periventricular leukomalacia, or | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | shunt for hydrocephalus has been confirmed yes at discharge. | |
| **Secondary outcomes at six weeks (corrected for gestational age)** | | | |
| Survival to six weeks corrected age | Derived from date of death (Death form) | Survival to six weeks met if no date of death recorded.<br><br>Confirmed no if a date of death before 6 weeks is recorded. | Risk Ratio (95% CI)<br>Risk Difference (95% CI) |
| Hospital visits (including day care and overnight admissions) up to 6 weeks of corrected age | Derived from resource use costs: hospital services (Six week questionnaire) | Sum of all hospital visits (not including the initial stay) recorded in the hospital services section of the six week questionnaire. | Descriptive |
| Breast-feeding at 6 weeks of corrected age | Derived from modes of feeding (Six week questionnaire) | Any infant for whom breastfeeding has been selected meets the outcome.<br><br>Confirmed no if breastfeeding has not been selected, and at least one other mode of feeding has been selected. | Descriptive |
| Mother's breast milk fed at 6 weeks of corrected age | Derived from types of feeding (Six week questionnaire) | Any infant for whom mother's breast milk has been selected meets the outcome. | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | Confirmed no if mother's breast milk has not been selected, and at least one other type of feeding has been selected. | |
| Parental satisfaction and wellbeing at 6 weeks of corrected age, using the Preterm Birth Experience and Satisfaction Scale (P-BESS) questionnaire | Preterm Birth Experience and Satisfaction Scale (P-BESS) | Scoreable if no more than two of the items are missing. In these situations missing data are imputed pro rata. | Difference in means (95% CI) |
| **Safety outcomes until full feeds** | | | |
| Number of blood glucose tests until full feed | Derived from Hypoglycemic Information (Daily Feed Log) | Sum of "Number of times blood glucose tested today?" | Descriptive |
| Number of tests indicating hypoglycaemia | Derived from Hypoglycemic Information (Daily Feed Log) | Sum of glucose test results <2.2 mmol/L. | Descriptive |
| Number of tests indicating severe hypoglycaemia | Derived from Hypoglycemic details. | Sum of glucose test results <1.0 mmol/L. | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| **Secondary outcome at 2 years (corrected for gestational age)** | | | |
| Survival to 2 years corrected age without moderate to severe neurodevelopmental impairment | Derived from the date of death (death form) and recorded neurodevelopmental impairment (parent-completed questionnaire/clinical follow-up assessment/NNRD) | Survival without moderate to severe neurodevelopmental impairment to two years corrected age met if no date of death recorded and no moderate to severe neurodevelopmental impairment recorded in any domain.<br>Confirmed no if a date of death or moderate to severe neurodevelopmental impairment in any one or more domain up to 2 years corrected age is recorded. | Risk ratio (95%CI)<br>Risk difference (95%) |
| Survival to 2 years corrected age | Derived from the date of death (death form) | Survival to 2 years met if no date of death recorded.<br><br>Confirmed no if a date of death up to 2 years is recorded. | Risk ratio (95%CI)<br>Risk difference (95%) |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| Moderate to severe neurodevelopmental impairment | Derived from the 2-year parent reported questionnaire/routine clinical assessment/NNRD | An infant is classified as having moderate to severe neurodevelopmental impairment if they have at least one of:<br><br>− moderate to severe cognitive impairment<br>− moderate to severe language impairment<br>− moderate to severe gross motor impairment<br>− moderate to severe hearing impairment<br>− moderate to severe visual impairment | Risk ratio (95%CI)<br>Risk difference (95%) |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| Moderate to severe cognitive impairment | Derived from the PARCA-R non-verbal cognitive scale (Questions 1-34 in 'Your child's play' section) | Assessed using PARCA-R.<br><br>The number of 'yes' responses of the 34 questions are summed to produce a total non-verbal cognitive raw score (range 0 – 34), which will then be converted into a standard score (normative mean 100: SD15) using the child's corrected age at assessment and sex.<br><br>Child with standard score < 70 can be classified as having moderate to severe cognitive impairment. | Descriptive |

| | | | |
|---|---|---|---|
| Moderate to severe language impairment | Derived from the PARCA-R language scale ('What your child can say' and 'How your child uses words') | Assessed using PARCA-R.<br><br>First component comprises of a 100-word vocabulary checklist, the words that child can say will sum to produce vocabulary subscale raw score (range 0 – 100).<br><br>Second component comprises of 18 questions, where the first 6 items and the remaining 12 items provide two subscale scores (both range 0 – 12). The sum of the two subscale scores yields a sentence complexity subscale raw score (range 0 – 24).<br><br>These two components can be summed to produce a total raw score for the language scale (range 0 – 124), which can then be converted to a standard score (normative mean 100; SD 15) using child's corrected age at assessment and sex.<br><br>A child with standard score < 70 can be classified as having moderate to severe language impairment. | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| Moderate to severe gross motor impairment | Derived from questions 3 and 4 in section 'Your child's health and physical development' (2 years questionnaire) | Confirmed yes if any one of the following is ticked:<br>- unable to walk even with help<br>- can only walk if helped by an adult or walking<br>- unable to sit<br>- can only sit with support or with help from an adult | Descriptive |
| Moderate to severe visual impairment | Derived from question 2 in section 'Your child's health and physical development' (2 years questionnaire) | Confirmed yes if any of the following is ticked:<br>- My child is able to see light only or is blind<br>- Is blind in one eye but had good vision in the other eye<br>- Has difficulty seeing even when wearing glasses | Descriptive |

| Outcome measures | Source | Derivation | Analysis metric |
|---|---|---|---|
| | | | |
| Moderate to severe hearing impairment | Derived from question 1 in section 'Your child's health and physical development' (2 years questionnaire) | Confirmed yes if child has a hearing aid or cochlear implant (or is on a waiting list for one), or any one of the following is ticked:<br><br>– my child is deaf<br>– has difficulty hearing even with a cochlear implant or hearing aid<br>– has a cochlear implant or hearing aid but hears well with it | Descriptive |

CI – Confidence Interval

## 3. INTERIM ANALYSIS

There are no formal interim analyses of clinical outcomes planned during the trial, hence no pre-planned design changes or provisions to avoid an inflation of the Type I error. The DMC will be provided with descriptive data by trial arm. Between-group estimates of differences in efficacy and/or safety outcomes may also be requested by the DMC following consideration of descriptive data provided by trial arm. Under such circumstances where unblinded information on efficacy is necessary, the impact on the Type I error will be properly taken into consideration. The DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be modified or terminated prematurely. If the TSC and sponsor decide that the recommended changes be implemented then this will be done via study protocol amendments.

The DMC will review the data on recruitment and adherence from the internal pilot and make recommendations to the TSC and the Trial Funders in respect of re-evaluating and adjusting methods for recruitment and adherence optimisation for the remaining timeline.

## 4. GENERAL ANALYSIS CONSIDERATIONS

### 4.1. Analysis sets

| **Outcome** | **Analysis set** |
|---|---|
| *Primary outcome* | *Primary analysis*<br>Participants will be analysed according to randomised group regardless of adherence to the allocated intervention. Main analysis will be for participants with outcome data collected (i.e. without imputation for missing data).<br><br>*Sensitivity analyses:*<br>A sensitivity analyses adjusting for baseline variables with marked imbalance will only include participants with outcome data collected (i.e. without imputation for missing data). |
| *Secondary outcomes* | Participants analysed according to randomised group regardless of adherence to the allocated intervention.<br>Main analysis for each outcome will be for participants with outcome data collected (i.e. without imputation for missing data). |
| *Safety outcomes*<br>*Adverse event* | Data will be presented according to:<br>• Participants analysed according to randomised group regardless of adherence to the allocated intervention.<br>• Participants analysed according to intervention received. |

Note: With the exception of parental satisfaction and wellbeing, the unit of analysis for all outcomes is the infant.

### 4.2. Estimands

The estimand for the primary outcome (length of hospital stay) will be the treatment policy estimand. The summary measure will be calculated as the difference in means between participants randomised

to full feeds versus gradual feeds, regardless of adherence to randomised allocation, in infants born 30-33 weeks gestation that survive to hospital discharge. The table below summarises the primary estimand.

| **Domain** | |
|---|---|
| Population | Premature infants born 30-33 weeks gestation |
| Outcome | Length of hospital stay |
| Treatment | **Intervention:** Full milk feeds enterally from day one<br>**Control:** Gradual milk feeds as per usual practice |
| Intercurrent event | Treatment switching/discontinuation – treatment policy<br><br>Death – principal stratum (excluded from the analysis) |
| Summary measures | Difference in mean days in hospital between the randomised groups. |

## 4.3. Timing of final analysis

All outcomes will be analysed collectively at the end of the trial.

## 4.4. Statistical software

All analyses will be performed using Stata version 18 or above.

## 4.5. Derived variables

| **Variable** | **Derivation** |
|---|---|
| **Gestational age (days)** | **Gestational age will be derived using the expected date of delivery (EDD) and infant's date of birth (DOB) collected at enrolment and calculated using:**<br><br>**280 – (EDD – DOB) = 280 – EDD + DOB** |
| **Gestational age (completed weeks)** | **(280 – EDD + DOB)/7 rounded down to the nearest integer** |
| **Adherence** | **Adherence to the intervention will be derived by totalling the number of hours IV fluids or parenteral nutrition prior to reaching full feeds, collected on the daily feed log.**<br><br>**Infants randomised to the intervention group will be considered adherent if they have received less than or equal to 24 hours of IV fluids or parenteral nutrition.**<br><br>**Infants randomised to the control group will be considered adherent if they have received more than 24 hours of IV fluids or parenteral nutrition, or if they have received IV fluids for exactly 24 hours where 'feeding regime meets expected criteria' checked under the form of Clinically Appropriate Alterations from Allocated Feeding Regime.** |
| **P-BESS total score and subscales** | **Questions are scored on a 5-point Likert scale, where a higher score indicates higher satisfaction with the care during the birth.**<br><br>**The total score will be derived as the sum of the scores for all 17 items.** |

| | |
|---|---|
| | **SUBSCALE 1 - INTERPERSONAL CARE:**<br>**Derived as the sum of items 2, 3, 4, 6, 7, 9, 17**<br><br>**SUBSCALE 2 - INFORMATION AND EXPLANATIONS:**<br>**Derived as the sum of items 1, 5, 8, 11, 13, 15, 16**<br><br>**SUBSCALE 3 - LACK OF CONFIDENCE IN STAFF:**<br>**Derived as the sum of items 10, 12, 14** |
| **PARCA-R standard score** | **PARCA-R score will be derived according to participant's corrected age at assessment and sex using the norm tables provided by the Parent Report of Children's Abilities-Revised (PARCA-R) manual.** |

## 4.6. Procedures for missing data

**Missing baseline data**
Missing baseline data is expected to be rare. However any missing baseline data in analyses using the baseline as a covariate will be imputed using the mean score at each centre in order to be able to include these participants in the analysis. These simple imputation methods are superior to more complicated imputation methods when baseline variables are included in an adjusted analysis to improve the precision of the treatment effect [5].

**Missing outcome data at discharge**
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).

It is expected there will be a small number of deaths prior to discharge, and these infants will be excluded from the primary analysis.

**Missing outcome data at six weeks**
The primary analysis will be based on participants with available data at six weeks with no imputation for participants with missing outcomes.

Missing data at six weeks will be reported by treatment group. Characteristics of participants with and without data at six weeks will also be described by treatment group.

**Missing outcome data at two years**
For non-verbal cognition scale, missing scores for questions will be imputed using the average of the score for the completed questions if no more than 4 questions are missing. If more than 4 questions are missing, a non-verbal cognition scale score cannot be calculated.

For language scale, unchecked/unanswered items for both vocabulary and sentence complexity sub-scales will be imputed zero. If all items are unchecked/unanswered for both sub-scales, then a language scale score cannot be calculated.

Missing data for outcomes at two years will be reported by treatment group. Characteristics of participants with and without data at 2 years will also be described by treatment group.

**Missing items in P-BESS**
Missing items on the P-BESS questionnaire will be imputed using the mean of the completed items for each participant, provided no more than 2 of the items are missing.

# 5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

## 5.1. Participant flow

The flow of mothers and infants through the trial will be summarised in a CONSORT diagram that will include the number of mothers and infants potentially eligible, number of mothers consenting,

numbers not randomised with reasons, numbers randomised to the two treatment groups, number of infants with primary outcome data at discharge, and the reasons if primary outcome was not available.

### 5.2. Baseline characteristics

Infants will be described by treatment group with respect to baseline demographic and clinical characteristics (including randomisation minimisation variables):

- Infant sex
- Infant age at randomisation
- Gestational age at delivery
- Birthweight
- Birthweight less than 10th centile for gestational age
- IV fluids started prior to randomisation
- Infant heart rate >100bpm at 5 mins
- Infant temperature on admission (°C)
- Infant worst base excess within first 24 hours of birth
- Infant receiving respiratory support at time of randomisation
- Reversed end diastolic flow on Maternal Doppler
- Multiple pregnancy
- Mother's age at randomisation
- Mother's ethnicity
- Mother received antenatal corticosteroids
- Mother received Magnesium Sulphate
- Caesarean section delivery
- Membranes ruptured >24h before delivery

Continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. No formal statistical comparisons will be made.

## 6. ASSESSMENT OF STUDY QUALITY

### 6.1. Randomisation

Randomisation will be minimised according to collaborating hospital; single or multiple birth; gestational age at birth, birthweight centile, and whether IV fluids were started prior to randomisation. Siblings from multiple pregnancies will be assigned to the same group.

The number of participants randomised to the two treatment groups at each recruiting centre will be tabulated. The other minimisation variables will be tabulated as part of the baseline characteristics.

### 6.2. Adherence

Adherence to the allocated intervention is defined:

- in the intervention group as infants who received less than or equal to 24 hours of IV fluids or parenteral nutrition prior to reaching full feeds
- in the control group as infants who received more than 24 hours of IV fluids or parenteral nutrition prior to reaching full feeds, or if they have received IV fluids for exactly 24 hours

where 'feeding regime meets expected criteria' checked under the form of Clinically Appropriate Alterations from Allocated Feeding Regime.

The number of infants that adhere to their allocated intervention (as defined above) will be summarised by treatment group in terms of frequency counts and percentages.

In addition, the following will be reported descriptively for both groups.

- The number of hours of IV fluids or parenteral nutrition prior to reaching full feeds
- Time from randomisation to first feed

Main reason for altering from the allocated feeding regime will be collected for infants who have not adhered to their allocated intervention. This will be reported descriptively by treatment groups.

### 6.3. Six week follow-up

Mothers and infants are followed up by a questionnaire at 6 weeks of age corrected for prematurity. The number and percentage of completed questionnaires will be tabulated in the two groups. The number of days to questionnaire completion from expected date of delivery will be summarised using the mean, median, lower & upper quartiles, minimum and maximum.

### 6.4. Two year follow-up

Infants are followed up by a questionnaire at 2 years of age corrected for prematurity. The number and percentage of completed questionnaires will be tabulated in the two groups. The number of days to questionnaire completion from expected date of delivery will be summarised using the mean, median, lower & upper quartiles, minimum and maximum.

### 6.5. Protocol deviations

A protocol deviation is a divergence or departure from the expected conduct of a study as defined in the protocol. Of particular importance are major deviations which may also be termed violations or non-compliances. These are deviations which may expose participants to increased risk, compromise the integrity of the entire study or affect participant eligibility.

The number of participants with protocol deviations as reported by researchers on the electronic case report form will be summarised by treatment group along with the type of deviation. Protocol deviations will also be listed.

## 7. ANALYSIS OF EFFECTIVENESS

### 7.1. Primary analysis

The primary comparative analysis will employ a mixed effects linear regression model 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. Multiple births will be nested within centre using random effects. All other minimisation variables will be adjusted for using fixed effects. The estimated between group effect will be presented using the adjusted difference between means, along with a 95% confidence interval and a p-value.

The default modelling approach will be to use an unstructured correlation matrix, but in the event of non-convergence a more parsimonious correlation matrix structure will be explored. The model assumptions will be checked by studying the residual plots and, if there are marked departures from the model assumptions then transformations to normalise the data or alternative analysis methods (e.g. Wilcoxon rank-sum test) will be investigated. We will also investigate the impact of outlying observations on the treatment effect estimate and apply alternative analysis methods if appropriate.

## 7.2. Sensitivity analysis of primary outcome

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).

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.

## 7.3. Subgroup analysis of primary outcome

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

| Subgroup | Levels |
|---|---|
| Gestation at birth | 30+0 to 30+6<br>31+0 to 31+6<br>32+0 to 32+6 |
| Birthweight centile adjusted for gestational age | <10$^{th}$ centile<br>≥10$^{th}$ 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 their corresponding 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.

## 7.4. Secondary outcomes

The following secondary outcomes will be analysed using appropriate mixed effects regression models depending on the type of outcome variable, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. Multiple births will be nested within centre using random effects. All other minimisation variables will be adjusted for using fixed effects. The between group effect will be reported using an appropriate adjusted effect estimate (See Table 1) along with a corresponding 95% confidence interval.

The analyses of secondary outcomes will be considered supportive to the primary outcome and estimates and confidence intervals, where presented, should be interpreted in this light.

### Binary outcomes

The following binary outcomes:

- Survival to hospital discharge

- Microbiologically-confirmed or clinically suspected late-onset sepsis
- Necrotising enterocolitis
- Any breast-feeding at hospital discharge
- Exclusive breast-feeding at hospital discharge
- Mother's breast milk fed at discharge
- Survival to six weeks
- Survival to two years without moderate to severe neurodevelopmental impairment
- Survival to 2 years corrected age
- Moderate to severe neurodevelopmental impairment

will be analysed using a mixed effects logistic regression model, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. Multiple births will be nested within centre using random effects. All other minimisation variables will be adjusted for using fixed effects, where possible[1]. The between group effect will be reported using an adjusted risk difference and adjusted risk ratio along with corresponding 95% confidence intervals for each. Point estimates and confidence intervals will be obtained using Stata's Margins command with standard errors computed using the delta method. [6] Individual components of the composite outcome at 2 years corrected age will be compared between treatment groups descriptively.

### Time to event outcomes

The following time to event outcomes

- Time to objective discharge criteria met
- Time to maintain full milk feeding
- Time to regain birth weight

will be compared between groups using a mixed effects parametric time-to-event model, adjusting for minimisation variables and accounting for the correlation between outcomes for infants born from a multiple pregnancy. Multiple births will be nested within centre using random effects. All other minimisation variables will be adjusted for using fixed effects. A parametric model has been chosen, as the semi-parametric Cox model does not allow for two levels of clustering to be specified. The conditional distribution of the response given the random effects will be assumed to be exponential, although the sensitivity of the results to this assumption will be explored. In particular, we will perform a sensitivity analysis using Cox regression and adjusting for clustering at the centre level only. Deaths prior to discharge will be excluded from the analysis. The between group effect will be reported using an adjusted hazard ratio along with a corresponding 95% confidence interval. Kaplan-Meier curves will be presented for each of the outcomes by trial arm.

### Growth z-scores corrected for gestational age at discharge (as per UK-NICM growth charts)

Weight, length, and head circumference will each be compared between groups using a mixed effects linear regression model, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. Multiple births will be nested within centre using random effects. All other minimisation variables will be adjusted for using fixed effects. The between group effect will be reported using the adjusted difference between means along with a corresponding 95% confidence interval. The unadjusted difference between means and 95% confidence interval will also be presented.

[1]As the binary outcomes are expected to be rare, it may not be possible to adjust for minimisation variables.

### Parental satisfaction and wellbeing

The unit of analysis for the P-BESS questionnaire is the mother. The total score from the P-BESS questionnaire will be compared between groups using a mixed effects linear regression model, adjusting for minimisation variables. Recruiting centre will be adjusted for using a random effect and all other minimisation variables will be adjusted for using fixed effects. The between group effect will be reported using the adjusted difference in means along with a corresponding 95% confidence interval. The P-BESS subscales

- Interpersonal care
- Information and explanations
- Lack of confidence in staff

will be reported descriptively by trial arm.

### Other secondary outcomes

All other secondary outcomes will be reported descriptively in each group without formal statistical comparisons. Continuous outcomes will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical outcomes will be summarised in terms of frequency counts and percentages.

## 7.5. Subgroup analysis of key secondary outcomes

Appropriate interaction terms will be included in the regression analyses for the following key secondary outcomes

- Microbiologically-confirmed or clinically suspected late-onset sepsis
- Necrotising enterocolitis (Bell stage 2 or 3)

in order to conduct subgroup analyses according to the following subgroups.

| Subgroup | Levels |
|---|---|
| Gestation at birth | 30+0 to 30+6<br>31+0 to 31+6<br>32+0 to 32+6 |
| Birthweight centile adjusted for gestational age | <10$^{th}$ centile<br>≥10$^{th}$ 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 in terms of the primary outcome rather than interactions of this kind on secondary outcomes, these subgroup analyses will be regarded as exploratory.

# 8. ANALYSIS OF SAFETY

## 8.1. Safety outcomes

The following safety outcomes will be summarised by treatment group using the mean, median, lower & upper quartiles, minimum and maximum. Infants will be analysed according to

- randomised group regardless of adherence with the allocated intervention.
- intervention received

| **Safety outcomes until full feeds** | | |
|---|---|---|
| Number of blood glucose tests until discharge | Derived from Hypoglycemic Information (Daily Feed Log) | Sum of "Number of times blood glucose tested today?" |
| Number of tests indicating hypoglycaemia | Derived from Hypoglycemic Information (Daily Feed Log) | Sum of glucose test results <2.2 mmol/L. |
| Number of tests indicating severe hypoglycaemia | Derived from Hypoglycemic details. | Sum of glucose test results <1.0 mmol/L. |

## 8.2. Adverse events

Any adverse events, serious adverse events, and suspected unexpected serious adverse reactions will be listed by trial arm.

Adverse events, serious adverse events, and suspected unexpected serious adverse reactions will be summarised in each group by the number of infants reporting adverse events and the number of events reported per infant.

A summary of the adverse events will be repeated for the infants according to their intervention received.

# 9. EXPLORATORY ANALYSIS

Total volume of each type of milk used for supplementing mother's breast milk before infants reach full feed will be summarised descriptively according to trial arm.

An additional non-randomised comparison will be carried out on the primary outcome and the following key secondary outcomes

- Survival to discharge
- Microbiologically-confirmed or clinically suspected late-onset sepsis (Bell stage 2 or 3)
- Necrotising enterocolitis

to compare infants who only received donor human milk and those who only received preterm formula milk to supplement mother's breast milk.

Infants will be described by supplementary feeding group with respect to baseline demographic and clinical characteristics.

A similar linear mixed effect regression model as used in the primary analysis, will be used to compare the mean length of stay between the two non-randomised groups, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. In addition, this model will adjust for trial arm and presence of absent or reversed end diastolic flow. In the event the two supplementary feeding groups are imbalanced with respect to any other baseline characteristics, the model will additionally adjust for these where possible. Multiple births will be nested within centre using random effects. All other variables will be adjusted for using fixed effects, where possible. The between group effect will be reported using an adjusted difference in means along with a corresponding 95% confidence interval.

Similarly,

- Survival to discharge
- Microbiologically-confirmed or clinically suspected late-onset sepsis (Bell stage 2 or 3)
- Necrotising enterocolitis

will be analysed using a mixed effects logistic regression model, adjusting for minimisation variables and accounting for correlation between outcomes for infants from multiple pregnancies. In addition, these models will adjust for trial arm and presence of absent or reversed end diastolic flow. Multiple births will be nested within centre using random effects. All other variables will be adjusted for using fixed effects. The between group effect will be reported using an adjusted risk ratio along with a corresponding 95% confidence interval.

# 10. REFERENCES

## 10.1. Internal references

| Document | Version | Date |
|---|---|---|
| FEED1 Protocol | 2.3 | 13-Apr-2023 |
| FEED1 dummy table | 2.0 | 03-Feb-2025 |

## 10.2. External references


[1] N Modi, et al., "A case definition for national and international neonatal bloodstream infection surveillance," *Arch Dis Child Fetal Neonatal Ed,* vol. 94(1), pp. F8-12, Jan 2009.

[2] R.C. Holman, et al., "Necrotising enterocolitis hospitalisations among neonates in the United States," *Paediatr Perinat Epidemiol,* vol. 20(6), pp. 498-506, Nov 2006.

[3] A Sawyer, et al., "Measuring parents' experiences and satisfaction with care during very preterm birth: a questionnaire development study," *BJOG,* vol. 121(10), pp. 1294-301, Sept 2014.

[4] S. I. Vidmar, et al., "Standardizing Anthropometric Measures in Children and Adolescents with Functions for Egen: Update," *Stata Journal,* vol. 13, pp. 366-378, 2013.

[5] T. R. Sullivan, et al., "Should multiple imputation be the method of choice for handling missing data in randomized trials?," *Stat Methods Med Res,* vol. 27(9), p. 2610–2626., Sept 2018.

[6] E. C. Norton, et al., "Computing Adjusted Risk Ratios and Risk Differences in Stata," *Stata Journal,* vol. 13(3), pp. 492-509, 2013.