

The neoGASTRIC Trial: Avoiding routine gastric residual volume measurement in neonatal critical care: a multi-centre randomised controlled trial

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The neoGASTRIC Trial: Avoiding routine gastric residual volume measurement in neonatal critical care: a multi-centre randomised controlled trial

Statistical Analysis Plan

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1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the NIHR HTA Programme and NHMRC-NIHR Collaborative Research Grant Scheme funded multicentre, pragmatic, unblinded, 2-arm, parallel group, randomised controlled neoGASTRIC trial, which aims to determine whether avoiding routine gastric residual volume measurement in preterm infants admitted to neonatal care reduces the time taken for an infant to reach full enteral feeds without increasing harm.

The results reported in these papers will follow the strategy set out here, and conforms to the published guidelines on the content for statistical analysis plans in clinical trials [1]. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis nor to prohibit accepted practices, but they are intended to establish the rules that will be followed as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees will be considered carefully, and carried out as far as possible in line with the principles of this analysis plan; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing.

2 BACKGROUND INFORMATION

2.1 Rationale

Routine measurement of gastric residual volume is the practice of regularly aspirating the entire stomach contents in order to assess the volume and colour of the gastric 'aspirate'. It is distinct from the aspiration of a small volume of gastric fluid for pH testing to confirm gastric tube position, which is recommended within national guidance for the use of nasogastric and orogastric feeding tubes [2]. The use of gastric feeding tubes is standard of care for preterm infants below approximately 34 gestational weeks [3-5].

Routine measurement of gastric residual volumes is established practice in many UK and Australian neonatal units [4]. The rationale underpinning this practice is to inform feeding decisions, to assess 'feed intolerance', and to predict and potentially prevent necrotising enterocolitis (NEC) [6, 7]. Despite evidence that gastric aspiration inaccurately measures gastric residual fluid volume [8] and is influenced by infant position and nasogastric tube size [9], its measurement remains deeply ingrained in many centres.

Potential adverse effects include delayed achievement of full enteral feeds [10, 11] with consequent risk of associated complications such as late-onset infection [12, 13] and longer neonatal unit stay [14, 15], discomfort/damage to gastric mucosa, which is a key concern to parents [16], and depletion of gastric secretions [17].

Although the routine measurement of gastric residual volumes is widely practised, there is large variation in how gastric residual volumes are interpreted and how they influence feeding decisions.

Full details of the rationale can be found in the protocol, in Section 1 – Introduction.

2.2 Objectives of the trial

The aim of this study is to determine whether avoiding the routine measurement of gastric residual volumes in preterm infants less than 34 weeks' gestation reduces the time taken for an infant to reach full milk feeds without increasing harms, up until discharge home or 44⁺⁰ gestational weeks^{+days}.

2.2.1 Primary objective

To determine if not routinely measuring gastric residual volumes compared to routine (up to 6-hourly) measurement of gastric residual volumes in preterm infants less than 34 weeks' gestation reduces the time to achieve full milk feeds, up until discharge home or 44⁺⁰ gestational weeks^{+days}.

2.2.2 Key secondary objective

To evaluate the impact of not routinely measuring gastric residual volumes compared to routine measurement of gastric residual volumes in preterm infants less than 34 weeks' gestation on rates of necrotising enterocolitis, up until discharge home or 44⁺⁰ gestational weeks^{+days}.

2.2.3 Other secondary objectives

- To evaluate the impact of not routinely measuring gastric residual volumes on other clinical outcomes.
- To evaluate the cost-effectiveness of not routinely measuring gastric residual volumes compared to routine measurement from an NHS perspective (analysis to be described in a separate Health Economics Analysis Plan (HEAP)).

2.3 Trial design

2.3.1 Overall design

Multi-centre, pragmatic, unblinded, 2-arm, parallel group, opt-out, randomised controlled trial, with an internal pilot (and embedded process evaluation), and an integrated health economic analysis.

2.3.2 Duration

Total duration 50 months (including a 12-month internal pilot and a total of 36 months recruitment).

2.4 Eligibility

2.4.1 Inclusion criteria

1. Gestational age at birth less than 34⁺⁰ gestational weeks^{+days} (up to and including 33⁺⁶ gestational weeks^{+days})
2. Nasogastric or orogastric tube in place

2.4.2 Exclusion criteria

1. Infant has received more than 15 ml/kg/day of milk for more than 24 hours
2. Gastrointestinal surgical condition (including suspected necrotising enterocolitis and focal intestinal perforation) prior to randomisation
3. Major congenital abnormalities
4. No realistic prospect of survival
5. A parent has opted out of infant's participation in neoGASTRIC

Infants enrolled in other interventional studies are eligible for participation in the neoGASTRIC trial.

2.5 Pathways of care

Two pathways of care are being compared; both represent standard clinical practice in different neonatal units in the UK and Australia. The allocated care pathway will be followed until the primary outcome is achieved, and thereafter:

- for as long as routine gastric measurement is standard local practice, although neonatal units are encouraged to continue the allocated care pathway until one of the 3 events below has occurred:
 - gastric feeding tubes are no longer required or,
 - the infant is discharged home or,

- o the infant reaches 44⁺⁰ gestational weeks^{+days}

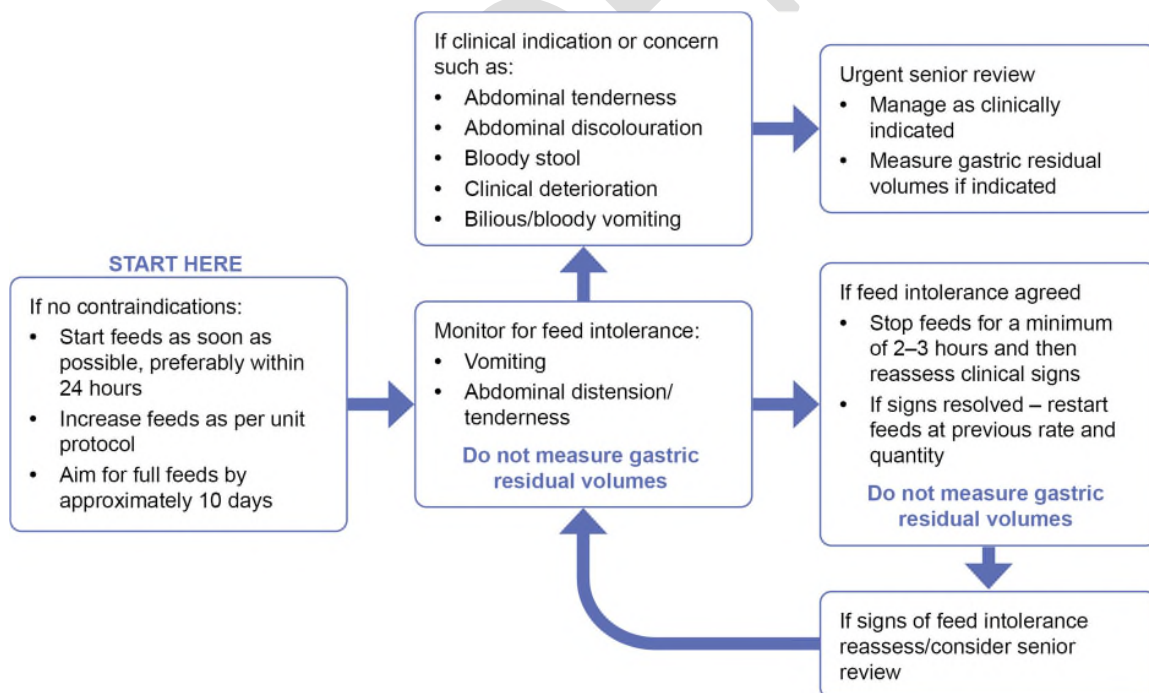
Where an infant develops a condition for which gastric residual measurement is clinically indicated – for example, suspected necrotising enterocolitis or suspected gastrointestinal obstruction – such gastric residual measurement is no longer ‘routine’, so should be undertaken as clinically indicated in both trial arms. When gastric residual measurement is no longer clinically indicated the infant should resume their allocated care pathway if this is considered clinically appropriate.

The two care pathways that will be compared are:

2.5.1 No routine measurement of gastric residual volumes (Figure 1)

Within this pathway of care, feed tolerance will be assessed by monitoring the infant for vomiting, abdominal tenderness, discolouration or distension, bloody stools or clinical deterioration (Figure 1). This pathway is based upon UK and international practice in units that do not routinely measure gastric residual volumes [4] and a consensus meeting [16] which involved parents, neonatologists, neonatal nurses, dieticians and trial methodologists.

Figure 1: Suggested management within the *No routine measurement of gastric residual volumes* pathway



2.5.2 Routine, up to 6-hourly, measurement of gastric residual volume

Within this pathway, gastric residual volumes will be measured at least every 6 hours and used to evaluate feed tolerance as specified by existing local practice. Where local practice is not standardised, units can use the neoGASTRIC trial-suggested gastric residual assessment

guidance in Appendix 1 of the Protocol (**Appendix 1: Suggested management within the 'Routine, up to 6-hourly, measurement of gastric residual volumes' pathway**).

2.6 Definition of primary and secondary outcomes

See section 6.1 for detail.

All outcomes will be measured up to discharge home or 44⁺⁰ gestational weeks^{+days} (whichever is sooner), unless otherwise stated.

2.6.1 Primary outcome (superiority outcome)

Time from birth to reach full milk feeds for 3 consecutive days (at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds)

2.6.2 Key secondary outcome (non-inferiority outcome)

NEC: modified Bell's stage 2 or greater [18], evaluated by Blinded Endpoint Review Committee (BERC)

2.6.3 Tested secondary outcomes

1. Severe NEC, confirmed at surgery or leading to death
2. All-cause mortality
3. Focal intestinal perforation
4. Gastrointestinal surgery
5. Late-onset infection (>72 hours after birth): microbiologically-confirmed [19, 20] or clinically suspected infection [21], evaluated by blinded endpoint review committee
6. Duration of neonatal unit stay, in days, including all levels of care
7. Duration of any parenteral nutrition, in days
8. Duration with a central venous line in situ, in days
9. Weight standard deviation score
10. Head circumference standard deviation score
11. Duration of invasive ventilation, in days
12. Chronic lung disease: receiving oxygen or respiratory support at 36 weeks' corrected gestation age
13. Retinopathy of prematurity: treated medically or surgically [22]
14. Brain injury on imaging: intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia [23]
15. Any vomiting resulting in feeds being withheld, up to 14 days from randomisation
16. Number of days feeds withheld at least once, up to 14 days from randomisation
17. Total number of hours feeds withheld, up to 14 days from randomisation
18. Breastfeeding
19. Receiving maternal breastmilk

Health economics outcomes will be defined in a separate HEAP.

2.6.4 Blinded Endpoint Review

Blinded endpoint review will be used for the following outcomes: modified Bell's stage 2 or greater NEC, late-onset infection, focal intestinal perforation and, where appropriate, time to full feeds. Blinded endpoint review will be conducted in accordance with a BERC Charter, written and agreed by the Project Management Group (PMG) and Trial Steering Committee (TSC). The BERC reviewers will comprise neonatal healthcare professionals who are expert in the fields for which blinded endpoint review data is being collected.

2.7 Hypothesis framework

For the primary outcome, and superiority secondary outcomes, the null hypothesis is that there is no difference in effect between the two trial arms. For the key secondary outcome, the null hypothesis is that no routine gastric residual volume is inferior to routine measurement by a risk difference of more than 1.5%.

2.8 Sample size & power

The planned sample size for this trial is 7040 infants (3520 per arm) individually randomised in approximately 36 Local Neonatal Units and Neonatal Intensive Care Units in the UK, and 4 tertiary neonatal units in Australia. Multiple births will be randomised to the same arm.

The primary outcome is time to full enteral feeds. The key secondary outcome is incidence of NEC, where the power to detect a meaningful non-inferiority margin is important. Data from the UK National Neonatal Research Database (NNRD) prior to the trial commencing demonstrated that the overall mean (SD) number of days to full enteral feeding in infants born <34 weeks of gestation is 9.4 (10.8) days and the incidence of significant NEC (requiring surgery, leading to death or recorded as part of the National Neonatal Audit Programme) is 3%. Based on data from other feeding trials [24, 25], we anticipate 30% multiple births; the intraclass correlation coefficient (ICC) for multiple birth sets will be 0.3 for time to full feeds and 0.05 for NEC.

2.8.1 Time to full enteral feeding

To detect a 1-day reduction in the time taken to reach full enteral feeding (important clinically and to parents) with 90% power and a two-sided 5% significance level, a sample size of 5088 (2544 per arm) is required. This has been inflated by 6% to account for the correlation in outcomes within multiple birth sets [24, 25]. A small level of crossover in the no routine measurement group is anticipated, with some measuring of gastric residuals occurring outside of the protocol guidelines; to allow for 10% crossover (non-adherence) the sample size has been inflated by 24% to obtain the same level of power [26]. Applying these inflation

rates and assuming a 5% attrition rate to discharge, the total number of infants required is 7040 (3520 per arm).

2.8.2 Moderate to severe necrotising enterocolitis

With a total sample size of 7040 and a control group event rate of 3%, the trial would have 92% power to detect a non-inferiority margin of no less than 1.5% in the treatment risk difference, with a 1-sided 2.5% significance level: non-inferiority can be claimed if the upper bound of the confidence interval of the treatment effect does not exceed 1.5%. These figures also allow for 10% crossover and 5% attrition. The inflation factor to account for the correlation in outcomes within multiple birth sets for NEC is 1% due to a lower ICC.

2.8.3 Update on sample size October 2025

A Data Monitoring Committee (DMC) meeting was held on 24 September 2025 and a TSC meeting on 15 October 2025. At these meetings, the sample size assumptions were assessed on data available for 5793 infants. At this time, the target recruitment was predicted to exceed the planned sample size of 7040 by the planned recruitment end date of 28 February 2026.

Following consultation with the DMC and TSC, it was agreed to continue recruiting until the planned end date of 28 February 2026, recognising that this may result in a higher final sample size. This decision was taken in line with independent oversight, and for methodological reasons to account for uncertainty in the initial sample size assumptions.

2.9 **Intervention allocation**

Randomisation of infants to either *no routine measurement of gastric residual volumes* or *up to 6-hourly measurement of gastric residual volumes* will be managed via a secure web-based randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU) (University of Oxford) with telephone backup available at all times (365 days per year). A Senior Trials Programmer at the NPEU CTU will write the web-based randomisation program and hold the allocation codes. The Senior Trials Programmer and a Senior Statistician will monitor implementation of the randomisation procedure throughout the trial. Randomisation reports will be provided to the DMC.

Randomisation will use a 1:1 allocation ratio. The randomisation program will use a probabilistic minimisation algorithm. To ensure balance between the randomised groups, minimisation criteria will include: hospital, multiple births (yes/no) and week of gestational age at birth.

2.9.1 Randomisation of multiple births

Infants that are part of a multiple birth set (twins or higher order multiples) will be randomised as a multiple: they will all be allocated to the same care pathway. This is based upon feedback from parent representatives, parent organisations including Bliss and the Twins Trust, and research involving parents and ex-preterm twins [27].

2.10 Data collection schedule

Trial data will be collected using electronic case report forms (CRFs) and either entered directly into the secure OpenClinica Clinical Database Management System (CDMS) or automatically transferred into it from the bespoke randomisation database. The individual participant data will be identified by a study participant number only. All data will be processed in line with the NPEU CTU Data Management SOPs.

All CRFs will be completed by research staff, with no forms completed by parents.

The CRFs to be completed for all participants are as follows:

- Entry Form
- Daily Feed Log
- Transfer/Discharge Form

Additional CRFs to be completed as required are as follows:

- Late-onset infections and gut signs form
- Serious Adverse Event (SAE) Report Form
- SAE Assessment Form
- SAE Processing Form
- Withdrawal Form
- Discontinuation Form

Follow-up will be until discharge home or 44⁺⁰ gestational weeks^{+days}, whichever is sooner. There will be no data collection after discharge home / 44⁺⁰ gestational weeks^{+days}.

Table 1 summarises the schedule of data collection and trial assessments.

Table 1: Schedule of events

TIMEPOINT	PERIOD						
	Enrolment		Treatment period				Close-out
	After birth	After eligibility confirmed	Day 1	Day 2	Day 3	etc.	Discharge from neonatal unit or 44 ⁺⁰ gestational weeks ^{+days}
ENROLMENT							
Eligibility screen	X						
Opt-out consent	X						
Randomisation		X					
Baseline data		X					
COMPARATOR PATHWAYS OF CARE							
<i>Routine or no measurement of gastric residual volumes</i>			X	X	X	X	
ASSESSMENTS							
Daily feeding log			X	X	X	X ¹	
Late-onset infection and gut signs						X ²	
DATA at DISCHARGE or 44 ⁺⁰ GESTATIONAL WEEKS ^{+DAYS}							
Clinical data ³							X ⁴

¹ Daily feeding logs until day 14, and then until the infant achieves full enteral feeds (at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds) for 3 consecutive days, or reaches 44+0 gestational weeks^{+days}

² Each episode of microbiologically-confirmed or clinically-suspected late-onset invasive infection, or if an 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, should be reported throughout the treatment period until hospital discharge

³ Clinical data is collected via the eCRF and (UK only) NNRD

⁴ If infant is withdrawn from the trial and parent/carer has asked for no further data collection, the *transfer/discharge* form can be completed at the time of withdrawal for data up until point of withdrawal

2.11 Data monitoring, interim analyses and stopping rules

Central monitoring will be used at NPEU CTU to monitor patterns of recruitment at sites and within the data, including data completeness and quality and safety reports. Outliers in the clinical data will be investigated and may trigger 'for cause' site monitoring.

2.11.1 Monitoring at local site

Direct access will be granted to authorised representatives from trial organisers, the research Sponsor and NHS Trusts to permit trial-related monitoring, audits and inspections.

2.11.2 The Data Monitoring Committee

A DMC independent of the applicants and of the TSC will review the progress of the trial at least once per year and provide advice on the conduct of the trial to the TSC and (via the TSC) to the funder, NPEU, sponsor and REC.

2.11.3 Interim analyses

Interim analyses will be presented to the DMC in the format of an Open Report and a Closed report. The Open Report will be prepared by the trial management team and the Closed Report will be prepared by the trial statistician. Full details of the contents of these reports are given in the DMC Charter.

It was agreed at the first meeting of the DMC that the results, by allocation, reviewed in the DMC closed session would be presented as groups X and Y and presented according to each stratum. The DMC will be provided an envelope at the meeting in order to unblind the allocation if required.

2.11.4 Stopping rules

A 12-month internal pilot study was undertaken in selected neonatal units to test and refine the components and processes of the study. The key progression criteria for the internal pilot were site and participant recruitment and adherence to the no routine measurement of gastric residual volume care pathway. Pre-defined stop-go criteria were considered by the TSC as a package to assess viability. Details for the pilot stop-go criteria can be found in the protocol, in Section 10 – Internal Pilot Study.

Additional to the pre-defined stop-go progression criteria, the TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety and efficacy. No formal statistical stopping guidelines will be employed, but a difference of at least 3 standard errors ($p < 0.001$, based on the Haybittle-Peto approach) in the interim analysis of a major outcome may be needed to justify halting or modifying the study prematurely.

2.12 Trial reporting

The trial will be reported according to the principles of the CONSORT statement, applying the CONSORT-Children and Adolescents (CONSORT-C) extension [28].

3 PROTOCOL DEVIATIONS

A protocol deviation is defined as a failure to adhere to the protocol such as the wrong intervention being administered, incorrect data being collected and documented, errors in applying inclusion/exclusion criteria, or missed follow-up visits due to error.

All protocol deviations will be listed in the final report. Protocol deviations are defined below.

3.1 Major

The following are pre-defined major protocol deviations with a direct bearing on the primary outcome:

- Data considered to be fraudulent

3.2 Minor

The following will be defined as minor protocol deviations:

Participants randomised in error

These include infants who, prior to randomisation:

- Were ≥ 34 weeks of gestation at birth
- Do not have a nasogastric or orogastric tube in place
- Have received more than 15 ml/kg/day of milk for more than 24 hours
- Have or have previously had a gastrointestinal surgical condition (included suspected necrotising enterocolitis and focal intestinal perforation)
- Have major congenital abnormalities
- Have no realistic prospect of survival
- Have a parent who has opted out of the infant's participant in neoGASTRIC

Intervention non-adherence

Adherence to trial intervention is measured up to the third consecutive day of full feeds, or when the infant reaches 44⁺⁰ weeks^{+days} gestational age, whichever is first.

Non-adherence for the purposes of the per protocol analysis and defining crossover will be defined as the following occurring on two or more consecutive calendar days:

No routine measurement of gastric residual volume: Two or more gastric residual volume measurements. Where gastric residual volume measurements are undertaken during assessment for a clinical indication or concern (as defined in the protocol Section 5.1) this will not be counted as non-adherence.

Routine measurement of gastric residual volume: Less than three gastric residual volume measurements.

For a detailed definition, see **Appendix 1 – Adherence data rules**.

4 ANALYSIS POPULATIONS

See Sections 6.1 and 6.2 for detailed definitions of the estimands.

4.1 Post-randomisation exclusions

Exclusions to the analysis post-randomisation are defined as any of the following:

- Infants for whom a parent has opted out of their infant's participation in neoGASTRIC
- Infants for whom consent is withdrawn by the parent(s) before any trial data is collected, i.e. infants whose only data available relates to randomisation processes
- Infants for whom an entire record of fraudulent data was detected (should fraudulent data be detected; consideration will be given to excluding all data for the site where such data were found).

The numbers and proportion of post-randomisation exclusions will be reported by randomised treatment group, and reasons summarised.

4.2 Population definitions

4.2.1 Modified intention to treat population

The modified intention to treat (ITT) population will be all infants randomised, excluding post-randomisation exclusions (see **Section 0 – Post-randomisation exclusions**)

4.2.2 Per protocol population

The per protocol (PP) population will be all infants randomised, excluding post-randomisation exclusions, and who were not classified as non-adherent to the intervention (see **Section 3.2 – Protocol Deviations: Minor**).

4.2.3 Safety population

The safety population will include all infants randomised.

5 DESCRIPTIVE ANALYSES

5.1 Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram [29]. This will describe the numbers of infants:

- Randomised
- Allocated to routine gastric residual volume measurements

- Did not follow routine gastric residual volume measurements pathway (with reasons), including the proportion non-adherent
- Allocated to no routine gastric residual volume measurements
 - Did not follow no routine gastric residual volume measurements pathway (with reasons), including the proportion non-adherent
- Randomised in error
- Withdrawn
- Post-randomisation exclusions (with reasons)
- Included in the modified ITT population
- Included in the PP population

5.2 Baseline comparability of randomised groups

Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean [SD] for normally distributed continuous variables, or median (interquartile [IQR] or entire range) for other continuous variables. There will be no tests of statistical significance performed for differences between randomised groups on any baseline variable.

A supplementary descriptive analysis will present baseline demographic factors and clinical characteristics against the UK population, using data from the NNRD for babies admitted to neonatal units in England, Scotland and Wales over the trial recruitment period who meet the trial gestational age inclusion criteria (gestational age at birth less than 34⁺⁰ gestational weeks^{+days}). This analysis will include infants in the UK only. There will be no tests of statistical significance performed for differences between the trial population and the UK population.

5.3 Losses to follow-up

Infants who are missing their primary outcome data will be considered lost to follow-up. The number and percentage of infants lost to follow-up will be reported with the reasons recorded.

6 COMPARATIVE ANALYSES

The routine up to 6-hourly measurement of gastric residual volumes group will be used as the reference group in all analyses.

6.1 Detailed definition of outcomes and estimands

6.1.1 Primary outcome

The primary outcome is the time from birth to reach full milk feeds for 3 consecutive days, measured in days. Full milk feeds is defined as at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds. An infant will be considered as having reached this endpoint on the third consecutive day of full milk feeds. The primary outcome population will include infants who were discharged home, reached 44⁺⁰ weeks^{+days} gestational age, or who died after reaching full milk feeds (babies who died before reaching the primary outcome will be excluded from the analysis of the primary outcome – see Table 2).

All information required to derive the primary outcome is recorded in the *Daily Feed Log*. If required, the BERC may determine the date at which an infant reached full milk feeds, should this not be easily derivable from the information available.

The process to derive the primary outcome is detailed in **Appendix 2 – Primary outcome data rules**.

6.1.1.1 Estimands framework

The primary outcome will be analysed under the estimands framework. For this, three intercurrent events [30, 31] have been identified for the primary outcome: deaths, non-adherence to intervention allocation, and reaching 44⁺⁰ gestational weeks^{+days} without reaching full feeds. Table 2 identifies the strategies to be used to handle these intercurrent events and the estimand (structured research question) for each of these for the primary analysis, with Table 3 identifying the strategies for the secondary analysis.

6.1.1.2 Withdrawals

Withdrawal from ongoing data collection is not considered an intercurrent event. However, a clear strategy for handling missing data resulting from withdrawal remains important within the estimand framework. For the primary outcome, infants withdrawn from ongoing data collection after reaching full feeds will be included in the both the primary and secondary analyses. Infants withdrawn before reaching full feeds will be considered to have missing primary outcome data in both the primary and secondary analyses.

Table 2: Estimand framework for the primary analysis of the primary outcome

Population	Preterm infants born less than 34 ⁺⁰ gestational weeks ^{+days} admitted to participating neonatal units in the United Kingdom and Australia
Treatment conditions	No routine measurement of gastric residual volumes (intervention) compared to routine measurement of gastric residual volumes (control)
Endpoint	Full milk feeds for 3 consecutive days (at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds). An infant will be considered as having reached this endpoint on the third consecutive day.
Summary measure	Mean difference
Handling of intercurrent events	<u>Event</u> : Deaths <u>Estimand strategy</u> : While alive (if an infant reaches full feeds before they die then they will be included; infants who die before they reach full feeds will not be included)
	<u>Event</u> : Any occurrences of non-adherence to the allocated intervention arm for any reason <u>Estimand strategy</u> : Treatment policy (all available outcome data will be used, regardless of adherence to intervention)
	<u>Event</u> : Reaching 44 ⁺⁰ gestational weeks ^{+days} without reaching full feeds <u>Estimand strategy</u> : Hypothetical (assume a hypothetical scenario that any surviving babies who have not reached full feeds by 44 ⁺⁰ gestational weeks ^{+days} will have reached full feeds the day after data collection stopped (44 ⁺¹ weeks ^{+days}))
Estimand (research question):	What is the mean difference in time to reach the third consecutive day of full milk feeds, among preterm infant born less than 34⁺⁰ gestational weeks^{+days} admitted to participating neonatal units in the United Kingdom and Australia, who did not have gastric residual volumes routinely measured compared to those who did have gastric residual volumes routinely measured, <i>excluding infants who died before reaching full milk feeds, regardless of adherence to allocated intervention arm, and assuming any infants who had not reached full milk feeds by 44⁺⁰ gestational weeks^{+days} would have done so on the next day (44⁺¹ weeks^{+days})?</i> This will be treated as an ITT analysis of a superiority outcome.

Table 3: Estimand framework for the secondary analysis of the primary outcome

Population	Preterm infants born less than 34 ⁺⁰ gestational weeks ^{+days} admitted to participating neonatal units in the United Kingdom and Australia
Treatment conditions	No routine measurement of gastric residual volumes (intervention) compared to routine measurement of gastric residual volumes (control)
Endpoint	Full milk feeds for 3 consecutive days (at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds). An infant will be considered as having reached this endpoint on the third consecutive day.
Summary measure	Mean difference
Handling of intercurrent events	<u>Event</u> : Deaths <u>Estimand strategy</u> : While alive (if an infant reaches full feeds before they die then they will be included; infants who die before they reach full feeds will not be included)
	<u>Event</u> : Any occurrences of non-adherence to the allocated intervention arm for any reason <u>Estimand strategy</u> : While on-treatment (infants will be excluded from the analysis if they had at least one episode of not adhering to allocated treatment arm for more than 2 consecutive days)
	<u>Event</u> : Reaching 44 ⁺⁰ gestational weeks ^{+days} without reaching full feeds <u>Estimand strategy</u> : Hypothetical (assume a hypothetical scenario that any surviving babies who have not reached full feeds by 44 ⁺⁰ gestational weeks ^{+days} , will have reached full feeds the day after data collection stopped (44 ⁺¹ weeks ^{+days}))
Estimand (research question):	What is the mean difference in time to reach the third consecutive day of full milk feeds, among preterm infant born less than 34⁺⁰ gestational weeks^{+days} admitted to participating neonatal units in the United Kingdom and Australia, who did not have gastric residual volumes routinely measured compared to those who did have gastric residual volumes routinely measured, <i>excluding infants who died before reaching full milk feeds, excluding infants who had any episodes of non-adherence to their allocated treatment arm for more than 2 consecutive days, and assuming any infants who had not reached full milk feeds by 44⁺⁰ gestational weeks^{+days} would have done so on the next day (44⁺¹ weeks^{+days})?</i> This will be treated as a PP analysis of a superiority outcome.

6.1.2 Key secondary outcome

The key secondary outcome is the number of babies who have NEC at modified Bell's stage 2 or greater, evaluated by BERC.

All information required to derive this outcome is recorded on the *Infections and Gut Signs* form. This form is completed by sites for each episode where an infant has signs of gastrointestinal pathology or has a confirmed or suspected late-onset infection. The BERC will review *Infections and Gut Signs* data for babies who have completed the trial and for whom at least one *Infection and Gut Signs* form has been received.

Further information on the role of the BERC can be found in the BERC Charter.

6.1.2.1 Estimands framework

Two intercurrent events have been identified for the key secondary outcome: deaths and non-adherence to treatment allocation. Table 4 identifies the strategies to be used to handle these intercurrent events and the estimand (structured research question) for both of these for the primary analysis, with Table 5 identifying the strategies for the secondary analysis.

6.1.2.2 Withdrawals

For the key secondary outcome, infants withdrawn from ongoing data collection after any BERC-confirmed NEC diagnosis will be included in both the primary and secondary analyses. Infants withdrawn before any BERC-confirmed NEC diagnosis will be considered to have missing key secondary outcome data.

Table 4: Estimand framework for the primary analysis of the key secondary outcome

Population	Preterm infants less than 34 ⁺⁰ weeks ^{+days} gestation admitted to participating neonatal units in the United Kingdom and Australia
Treatment conditions	No routine measurement of gastric residual volumes (intervention) compared to routine measurement of gastric residual volumes (control)
Endpoint	NEC at modified Bell's stage 2 or greater confirmed by the BERC
Summary measure	Risk difference
Handling of intercurrent events	<u>Event</u>: Deaths <u>Estimand strategy</u>: Treatment policy (if an infant died with no evidence of NEC before or at death then this infant is included and counted as not having a diagnosis of NEC. This includes infants who have no <i>Infection & Gut Signs</i> forms completed, and infants with <i>Infection & Gut Signs</i> forms completed and where BERC was carried out)
	<u>Event</u>: Any occurrences of non-adherence to the allocated intervention arm for any reason <u>Estimand strategy</u>: While on-treatment (infants will be excluded from the analysis if they had at least one episode of not adhering to allocated treatment arm for more than 2 consecutive days)
Estimand (research question):	What is the risk (as a difference) of an infant having confirmed necrotising enterocolitis (NEC), among preterm infant born less than 34⁺⁰ gestational weeks^{+days} admitted to participating neonatal units in the United Kingdom and Australia, who did not have gastric residual volumes routinely measured compared to those who did have gastric residual volumes routinely measured, <i>assuming infants who died without evidence of NEC before or at death did not have NEC and excluding infants who had any episodes of non-adherence to their allocated treatment arm for more than 2 consecutive days?</i> This will be treated as a PP analysis of a non-inferiority outcome.

Table 5: Estimand framework for the secondary analysis of the key secondary outcome

Population	Preterm infants less than 34 ⁺⁰ weeks ^{+days} gestation admitted to participating neonatal units in the United Kingdom and Australia
Treatment conditions	No routine measurement of gastric residual volumes (intervention) compared to routine measurement of gastric residual volumes (control)
Endpoint	NEC at modified Bell's stage 2 or greater confirmed by the BERC
Summary measure	Risk ratio/Risk difference
Handling of intercurrent events	<u>Event</u> : Deaths <u>Estimand strategy</u> : Treatment policy (if an infant died with no evidence of NEC before or at death then this infant is included and counted as not having a diagnosis of NEC)
	<u>Event</u> : Any occurrences of non-adherence to the allocated intervention arm for any reason <u>Estimand strategy</u> : Treatment policy (all available outcome data will be used, regardless of adherence to intervention)
Estimand (research question):	What is the risk (as a ratio/difference) of an infant having confirmed necrotising enterocolitis (NEC), among preterm infant born less than 34⁺⁰ gestational weeks^{+days} admitted to participating neonatal units in the United Kingdom and Australia, who did not have gastric residual volumes routinely measured compared to those who did have gastric residual volumes routinely measured, <i>assuming infants who died without evidence of NEC before or at death did not have NEC and regardless of adherence to allocated intervention arm?</i> This will be treated as an ITT analysis of a non-inferiority outcome.

6.1.3 Other tested secondary outcomes

6.1.3.1 Withdrawals

For each other secondary outcome, infants who are withdrawn from ongoing data collection after reaching the endpoint for that outcome will be included in the primary and secondary analyses, where relevant. Infants who are withdrawn before reaching the endpoint for a secondary outcome will be treated as having missing data for that outcome.

Table 6: Detailed outcome definitions and analysis populations for tested secondary outcomes

Outcome	Definition	Outcome type	Analysis population
[1] Severe NEC, confirmed at surgery or leading to death	The number of infants who had severe NEC which was confirmed at surgery or led to death, as evaluated by the BERC.	Binary	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. Deaths If an infant died with no evidence of NEC before or at death then this infant is included and counted as not having a diagnosis of NEC. This includes infants who have no <i>Infection & Gut Signs</i> forms completed, and infants with <i>Infection & Gut Signs</i> form completed and where BERC was carried out. Non-adherence <i>Primary analysis:</i> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <i>Secondary analysis:</i> Infants will be excluded from the analysis if they had at least one episode of not adhering to allocated treatment arm for more than 2 consecutive days (PP principal).
[2] All-cause mortality	The number of infants who died from any cause.	Binary	All infants up to discharge home or 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. Non-adherence <i>Primary analysis:</i> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <i>Secondary analysis:</i> Infants will be excluded from the analysis if they had at least one episode of not adhering to allocated treatment arm for more than 2 consecutive days (PP principal).
[3] Focal intestinal perforation	The number of infants who had at least 1 episode of focal intestinal perforation, as evaluated by the BERC.	Binary	As for Severe NEC (primary and secondary analysis).
[4] Gastrointestinal surgery	The number of infants who had any gastrointestinal surgery.	Binary	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. Deaths If an infant died with no evidence of gastrointestinal surgery before or at death then this infant is included and counted as not having had gastrointestinal surgery. Non-adherence All available outcome data will be used, regardless of adherence to intervention (ITT principal).
[5] Late-onset infection (>72 hours after birth): microbiologically	The number of infants with at least one episode of either	Binary	As for Severe NEC (primary analysis only).

Outcome	Definition	Outcome type	Analysis population
confirmed or clinically suspected infection	microbiologically confirmed or clinically suspected late-onset infection, as evaluated by the BERC.		
[6] Duration of neonatal stay, in days, including all levels of care	Cumulative total number of days an infant was an inpatient in a neonatal unit, including all levels of care, in survivors only.	Continuous	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will not contribute to the analysis population. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Reaching 44⁺⁰ weeks^{+days}</u> Any surviving infant who was still inpatient at 44⁺⁰ weeks^{+days} gestational age will be assumed to have been discharged the day after data collection stopped (44⁺¹ weeks^{+days}), unless a date of discharge is available.
[7] Duration of any parenteral nutrition, in days	Cumulative total number of days an infant was receiving any parenteral nutrition, in survivors only.	Continuous	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Reached 44⁺⁰ weeks^{+days}</u> Any surviving infants who were still receiving parenteral nutrition at 44⁺⁰ weeks^{+days} gestational age will be assumed to have stopped receiving this the day after data collection stopped (44⁺¹ weeks^{+days}).
[8] Duration with a central venous line in situ, in days	Cumulative total number of days an infant had a central venous line in situ, in survivors only.	Continuous	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Reached 44⁺⁰ weeks^{+days}</u> Any surviving infants who still had a central venous line in situ at 44⁺⁰ weeks^{+days} gestational age will be assumed to have had this removed the day after data collection stopped (44⁺¹ weeks^{+days}).
[9] Weight standard deviation score	The standard deviation score (z-score) for the infant's weight-for-age, measured	Continuous	All infants who were discharged home or reached 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded.

Outcome	Definition	Outcome type	Analysis population
	closest to their endpoint, in survivors only.		<u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal).
[10] Head circumference standard deviation score	The standard deviation score (z-score) for the infant's head circumference-for-age, measured closest to their endpoint, in survivors only.	Continuous	As for Weight standard deviation score .
[11] Duration of invasive ventilation, in days	Cumulative total number of days an infant was receiving invasive ventilation, in survivors only.	Continuous	All infants who were discharged home or reached 44 ⁺⁰ weeks ^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Reached 44⁺⁰ weeks^{+days}</u> Any surviving infants who were still receiving invasive ventilation at 44 ⁺⁰ weeks ^{+days} gestational age will be assumed to have stopped receiving this the day after data collection stopped (44 ⁺¹ weeks ^{+days}).
[12] Chronic lung disease (CLD): receiving oxygen or respiratory support at 36 weeks' corrected gestational age	The number of infants receiving oxygen or respiratory support at 36 weeks corrected gestational age.	Binary	All infants who did not die or withdraw before reaching 36 ⁺⁰ weeks ^{+days} corrected gestational age. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Age-related risk</u> <i>Primary analysis:</i> To account for the risk of developing CLD being age-related, any infants who were not born before 32 ⁺⁰ weeks ^{+days} gestation will be assumed as not having CLD (included as '0' / 'No'). <i>Secondary analysis:</i> Infants who were not born at less than 32 ⁺⁰ weeks ^{+days} gestation will be excluded.
[13] Retinopathy of prematurity (ROP), treated medically or surgically	The number of infants who had any ROP which was treated medically or surgically.	Binary	All infants who were discharged home or reached 44 ⁺⁰ weeks ^{+days} gestational age, whichever is sooner. <u>Deaths</u> If an infant died with no evidence of ROP treated medically or surgically before or at death then this infant is included and counted as not having had ROP. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal). <u>Age-related risk</u> <i>Primary analysis:</i> To account for the risk of developing ROP being age-related, any infants not born before 31 ⁺⁰

Outcome	Definition	Outcome type	Analysis population
			weeks^{+days} in the UK, or either before 32⁺⁰ weeks^{+days} or weighing under <1500g in Australia, will be assumed to not have ROP (included as '0'/'No') as they will not have required risk-based screening <i>Secondary analysis:</i> Infants not born before 31⁺⁰ weeks^{+days} in the UK, or either before 32⁺⁰ weeks^{+days} or weighing under <1500g in Australia will be excluded.
[14] Brain injury on imaging: intraventricular haemorrhage (IVH) grade 3 or 4 and/or cystic periventricular leukomalacia (cPVL)	The number of infants with any post-randomisation diagnosis of intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia.	Binary	As for Gastrointestinal surgery .
[15] Any vomiting resulting in feeds being withheld, up to 14 days from randomisation	Number of infants with vomiting resulting in feeds being withheld.	Binary	All randomised infants. <u>Deaths</u> All data from infants who died within 14 days post-randomisation will be included up to the date of death. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal).
[16] Number of days feeds withheld at least once, up to 14 days from randomisation	Total number of days feeds withheld at least once among all babies allocated to this pathway of care.	Continuous	As for Any vomiting resulting in feeds being withheld .
[17] Total number of hours feeds withheld, up to 14 days from randomisation	Total number of hours feeds withheld at least once among all babies allocated to this pathway of care.	Continuous	As for Any vomiting resulting in feeds being withheld .
[18] Breastfeeding	The number of infants breastfeeding at discharge home or 44 ⁺⁰ weeks ^{+days} gestational age, whichever is sooner, in survivors only.	Binary	All infants who survived to discharge home or 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded. <u>Non-adherence</u> All available outcome data will be used, regardless of adherence to intervention (ITT principal).
[19] Receiving maternal breastmilk	The number of infants receiving any maternal breastmilk at discharge home or 44 ⁺⁰ weeks ^{+days} gestational age,	Binary	All infants who survived to discharge home or 44⁺⁰ weeks^{+days} gestational age, whichever is sooner. <u>Deaths</u> Infants who died before reaching either timepoint will be excluded. <u>Non-adherence</u>

Outcome	Definition	Outcome type	Analysis population
	whichever is sooner, in survivors only.		All available outcome data will be used, regardless of adherence to intervention (ITT principal).

Detailed derivations for the primary outcome are given in **Appendix 2**. Detailed derivations for all other outcomes will be described in a separate data derivation document.

6.2 Primary analysis

The primary analysis of all outcomes except the key secondary outcome will be based on a modified ITT approach; infants with outcome data will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or procedure received. For the key secondary outcome (non-inferiority outcome) the primary analysis will be based on a PP population, and with infants analysed in the groups to which they are assigned.

The primary outcome and other continuous outcomes will be summarised with means and standard deviations where normally distributed, or median and interquartile ranges where non-normally distributed. Continuous tested outcomes will be analysed using mixed linear regression with mean differences and confidence intervals presented, where model assumptions are satisfied. Where continuous tested outcomes are skewed, the first step will be to address this will be to use bootstrapping of the confidence intervals, using at least 1000 repetitions. For severely skewed continuous outcomes, or outcomes where bootstrapping is not deemed appropriate, quantile regression models will be used, with median differences and confidence intervals presented. The primary outcome will also have a Kaplan-Meier plot produced using a time-to-event analysis. For this, a Cox-regression model will be fitted, with infants entering on the day of birth and exiting when they are discharged, reach 44⁺⁰ weeks^{+days}, are withdrawn with no further data collection, or die before reaching full feeds (right censoring). An event will occur when an infant reaches full feeds according to the definition in Appendix 2. Survival tables will not be presented alongside this plot.

Binary outcomes, including the key secondary outcome, will be summarised with counts and percentages. For binary tested outcomes, risk ratios and confidence intervals will be calculated using a mixed binomial, or Poisson model with a log link if the binomial model fails to converge. Risk differences and associated confidence intervals will also be calculated using a mixed binomial model with an identity link, or Poisson model with identity link if the binomial model fails to converge.

Analyses will be adjusted for the randomisation minimisation factors where possible (centre, week of gestation at birth as a continuous outcome, and multiple birth). Centre will be treated as a random effect in the model, and all other factors as fixed effects. Correlation between siblings from multiple births will be accounted for by nesting the 'multiple' cluster within

centre, where technically possible. Where the model fails to converge due to this nesting, multiple births will be included in the model as a random effect and centre will be included as a fixed effect. Both crude and adjusted effect estimates and corresponding 95% confidence intervals will be presented, but the primary inference will be based on the adjusted estimates.

6.3 Secondary analyses

Secondary analyses will be carried out using the PP population for the primary outcome and for the severe NEC, focal intestinal perforation, and all-cause mortality secondary outcomes, as described in Tables 3 and 6. A secondary analysis for the key secondary outcome will be carried out using the modified ITT population (Table 5).

To account for the age-specific risk of CLD (36^{+0} weeks^{+days} gestation), a secondary analysis will be carried out restricted to infants born before 32^{+0} weeks^{+days} gestation. Similarly, to account for the age-specific risk of developing ROP, a secondary analysis will be carried out restricted to infants born before 31^{+0} weeks^{+days} gestation in the UK, and infants either born before 32^{+0} weeks^{+days} or weighing under <1500g in Australia.

The treatment effects for secondary analysis of the primary and key secondary outcomes will be presented with 95% confidence intervals and p-value. The treatment effects for secondary analyses of secondary outcomes will be presented with 95% confidence intervals, and without any p-values.

6.4 Pre-specified subgroup analyses

The consistency of the treatment effect on the primary outcome and key secondary outcome will be assessed across pre-specified subgroups of infants using the statistical test of interaction. Effect estimates and 95% confidence intervals will be presented for each subgroup, along with the interaction p-value.

The subgroup categories are:

- gestational age group at birth ($< 28^{+0}$, 28^{+0} to 31^{+6} , and $\geq 32^{+0}$ weeks^{+days})
- birth weight (<10 th centile for gestational age, ≥ 10 th centile for gestational age)
- sex (male, female, indeterminate)
- country (UK, Australia)

Additionally, the summary statistics for all outcomes will be presented by country, ethnicity and IMD decile (UK infants only).

6.5 Sensitivity analyses

Baseline characteristics and some outcome data will also be available from the NNRD for all UK-based participants. This data will be used to impute any missing values for variables where it is available (see **Section 6.7 - Missing data**). A sensitivity analysis will be carried out where any data which has been imputed from the NNRD data is excluded.

Co-enrolment to the FEED1 trial, investigating full exclusively enteral fluids from day 1 versus gradual feeding in preterm infants, has been permitted. A sensitivity analysis will be carried out repeating the primary analysis of both the primary and key secondary outcomes, excluding infants who were also recruited to the FEED1 trial.

6.6 Significance levels and adjustment of p-values for multiplicity

95% confidence intervals will be used for all pre-specified outcome comparisons including subgroup analyses. P-values will be presented for the adjusted primary and secondary analyses of the primary outcome only. No unadjusted p-values will be presented. No adjustments to p-values will be made for multiplicity.

6.7 Missing data

Missing data will be described, for example, by presenting the number of individuals in the missing category. Missing data as a result of infants being lost to follow-up is expected to be minimal for short term outcomes.

Data from the NNRD will be used to impute any missing data for descriptive and outcome variables for infants recruited in the UK and where the outcomes are included in the NNRD dataset. The number of infants for whom missing data were imputed using NNRD data will be reported for each variable, where this occurred for at least one infant. This will include the outcomes:

- Time to reach full milk feeds (primary outcome)
- All-cause mortality
- Gastrointestinal surgery
- Duration of neonatal stay, including all levels of care
- Duration of any parenteral nutrition
- Duration with a central venous line in situ
- Weight SD score
- Head circumference SD score
- Duration of invasive ventilation
- Retinopathy or prematurity, treated medically or surgically

- Breastfeeding
- Receiving maternal breastmilk

6.8 Statistical software employed

All analyses will be conducted on validated statistical software such as Stata/SE version 18 (or later) or R version 4.4.2 (or later).

7 SAFETY DATA ANALYSIS

Serious adverse events (SAEs) will be listed by allocation.

7.1 Foreseeable SAEs which do not require expedited reporting via an SAE form

The following events are expected in the population, and information will be collected by recruiting sites during the intervention period as outcomes, therefore they do not require reporting as SAEs. Data pertaining to these events will be reviewed by the DMC at a frequency to be determined by the DMC (at least annually).

- Death (unless cause not anticipated in this population)
- NEC or gastrointestinal perforation
- Bronchopulmonary dysplasia or chronic lung disease
- Late-onset infection
- Brain injury on imaging: intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia

7.2 Foreseeable SAEs relating to known complication(s) of prematurity

Any serious event that is deemed by the investigator to be a known complication of prematurity at that gestational age should not be reported as an SAE but should be recorded in the infant's medical notes, as per usual practice. They do not require reporting by trial centres as SAEs unless considered that they may be causally related to the allocated pathway of care, in which case they must be reported as detailed in Section 8.2.5 of the protocol.

8 ADDITIONAL EXPLORATORY ANALYSIS

Any analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan. Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such.

The treatment effects for any exploratory analyses will be presented with 95% confidence intervals where appropriate, and without any p-values.

9 DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

None yet.

10 REFERENCES

10.1 Trial documents

- neoGASTRIC Dummy tables
- neoGASTRIC Data derivation document

10.2 Other references

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11 APPENDIX 1 – ADHERENCE DATA RULES

Adherence to trial intervention is only measured up to the third consecutive day of full feeds, or when the infant reaches 44⁺⁰ weeks^{+days} gestational age, whichever is first.

Non-adherence for the purposes of the per protocol analysis and defining crossover will be defined as the following occurring on two or more consecutive calendar days:

No routine measurement of gastric residual volume: Two or more gastric residual volume measurements. Where gastric residual volume measurements are undertaken during assessment for a clinical indication or concern (as defined in **Protocol Section 5.1**) this will not be counted as non-adherence.

Routine measurement of gastric residual volume: Less than four gastric residual volume measurements.

The below table indicates the data rules to be applied to determine whether an infant was non-adherent using data recorded in the *Daily Feed Logs*, by treatment arm.

Arm of trial	Query management
Both arms of the trial:	
Day 0 should be ignored for adherence <i>(as this the day of randomisation and therefore is often a partial day on the trial)</i>	No queries for adherence raised in OpenClinica for Day 0
On the days infant is NBM, constraints around adherence are ignored	If the question 'Was the infant nil by mouth' is answered yes, then number of GRV measurements that day is ignored
Infants on Routine GRV arm	
If infant is establishing oral feeds, then aspirating may not occur, so on these dates constraints around adherence are ignored On the days that a tube is not in place constraints around adherence are ignored	No query raised in OpenClinica if 'Is infant establishing oral feed' is answered yes and <4 GRV measurements recorded No query to be raised in OpenClinica if 'Does the infant have a gastric tube in situ today' = no and <4 GRV measurements recorded
Infants in No Routine GRV arm	
If any gastric residuals were measured due to clinical indication or concern, these will not count as non-adherence	If total GRV measurements minus total measured for clinical indication or concern = 0 (i.e. they were all measured for clinical indication or concern), no query is triggered

12 APPENDIX 2 – PRIMARY OUTCOME DATA RULES

The time from birth to reach full milk feeds for 3 consecutive days (at least 145 ml/kg/day where this is considered full enteral feeds, or where breastfeeding and any additional milk is considered equivalent to full enteral feeds) is primarily recorded in the *Daily Feed Log*. Within this log, sites record:

- Whether an infant has reached full feeds by the primary outcome definition, as a binary yes/no response
- The weight of the infant being used to calculate the volume of fluids/feeds given that day, in grams
- The total milk volume the infant received that day, in millilitres
- Whether the infant was breastfed on that day, as a binary yes/no response

The weight of the infant and the total milk volume recorded on the *Daily Feed Log* is then used to auto-calculate the milk feeds received that day in ml/kg/day.

Daily feed volumes are also recorded on the NNRD, and this data may be used to impute days where information is missing from the *Daily Feed Logs*.

The below table indicates the derivation the primary outcome from the available data sources.

Data source	Derivation
Daily Feed Log	
'Has the infant reached full feeds today' is yes for 3 consecutive days but the calculated volume of feeds is <145ml/kg/day for any of those days AND breastfeeding is yes on the days where volume <145ml/kg/day.	Include as reaching full feeds.
'Has the infant reached full feeds today' is yes for 3 consecutive days but calculated volume of feeds is <145ml/kg/day for any of those days AND breastfeeding is not ticked on the days where volume <145ml/kg/day.	Do not include as reaching full feeds
'Has the infant reached full feeds today' is no but volume recorded per day is ≥145ml/kg/day for 3 consecutive days. OR 'Has the infant reached full feeds today' response is missing, but feed volume is ≥145ml/kg/day for 3 consecutive days.	Include as reaching full feeds.
'Has the infant reached full feeds today' is yes for 3 consecutive days but the calculated volume of feeds is missing for those same days.	Include as reaching full feeds.
NNRD	
If date full feeds reached cannot be derived using the Daily Feed Logs, data available on the NNRD will be used.	Using the daily volume (ml) and the daily working weight (g), feed volume will be calculated for each day. Full feeds will have been reached where feed volume is ≥145ml/kg/day for 3 consecutive days.

13 APPROVAL

Senior Statistician	Name: Heather O'Connor	
	Signature <i>Heather O'Connor</i> <u>Heather O'Connor (Jul 20, 2026 09:35:32 GMT+1)</u>	Date Jul 20, 2026
Chief Investigator	Name: Professor Chris Gale	
	Signature <i>[Signature]</i> <u>Chris Gale (Jul 17, 2026 18:06:39 GMT+1)</u>	Date Jul 17, 2026
Australian Chief Investigator	Name: Dr Calum Roberts	
	Signature <i>Calum Roberts</i> <u>Calum Roberts (Jul 20, 2026 08:00:08 GMT+10)</u>	Date Jul 20, 2026
SAP Reviewer	Name: Pollyanna Hardy	
	Signature <i>[Signature]</i>	Date Jul 20, 2026

14 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to interim analysis/monitoring /unblinding
0.1	26/07/2023	HO	First draft created by HO	Before first interim analysis (for DMC reporting)
0.2	29/08/2024	HO	Updated following Statistics Meeting, with CG, PH and EN.	After first interim analysis (for DMC reporting)
0.3	18/02/2026	HO	Updated following Statistics Meeting, with CG and PH. Includes estimands for the primary and key secondary outcome, with additional detail added to the descriptions for all other outcomes. Updated to account for discussions within PMG meetings.	After first interim analysis (for DMC reporting)
0.4	24/06/2026	HO	Updated following review by CR, CG and PH.	After first interim analysis (for DMC reporting)
0.5	14/07/2026	HO	Updated followed review by the wider CIG.	After first interim analysis (for DMC reporting)
1.0	17/07/2026	HO	Generation of V1.0.	After first interim analysis (for DMC reporting). Before final database lock.

neoGASTRIC_SAP_v1.0_17Jul2026

Final Audit Report

2026-07-20

Created:	2026-07-17
By:	Heather O'Connor (heather.oconnor@npeu.ox.ac.uk)
Status:	Signed
Transaction ID:	CBJCHBCAABAAtnAJnMYoHVD6SmnA67yXme67iNRruFMo

"neoGASTRIC_SAP_v1.0_17Jul2026" History

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2026-07-17 - 4:47:44 PM GMT
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