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

Protocol

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Chief Investigator:	Professor Chris Gale Signature and date _____
Australian Chief Investigator:	Dr Calum Roberts Signature and date _____
Trial Statistician:	Pollyanna Hardy, NPEU CTU Signature and date _____
Trial Coordination Centre:	For general queries and supply of trial documentation please contact: Trial Manager National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU) Nuffield Department of Population Health University of Oxford

Old Road Campus
Oxford OX3 7LF
Tel: 01865 617927
Email: neogastric@npeu.ox.ac.uk

Clinical Queries

Clinical queries should be directed to Professor Chris Gale (CI) who will direct the query to the appropriate person

Professor Chris Gale
Address: Neonatal Medicine
Chelsea and Westminster Hospital Campus
4th floor, lift bank D
369 Fulham Road
London, SW10 9NH
Email: christopher.gale@imperial.ac.uk

Sponsor

Imperial College London is the research Sponsor for this trial. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary's Hospital
Praed Street
London
W2 1NY
Tel: 0207 594 1872

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This protocol describes the neoGASTRIC study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

TABLE OF CONTENTS

Appendices

GLOSSARY OF ABBREVIATIONS

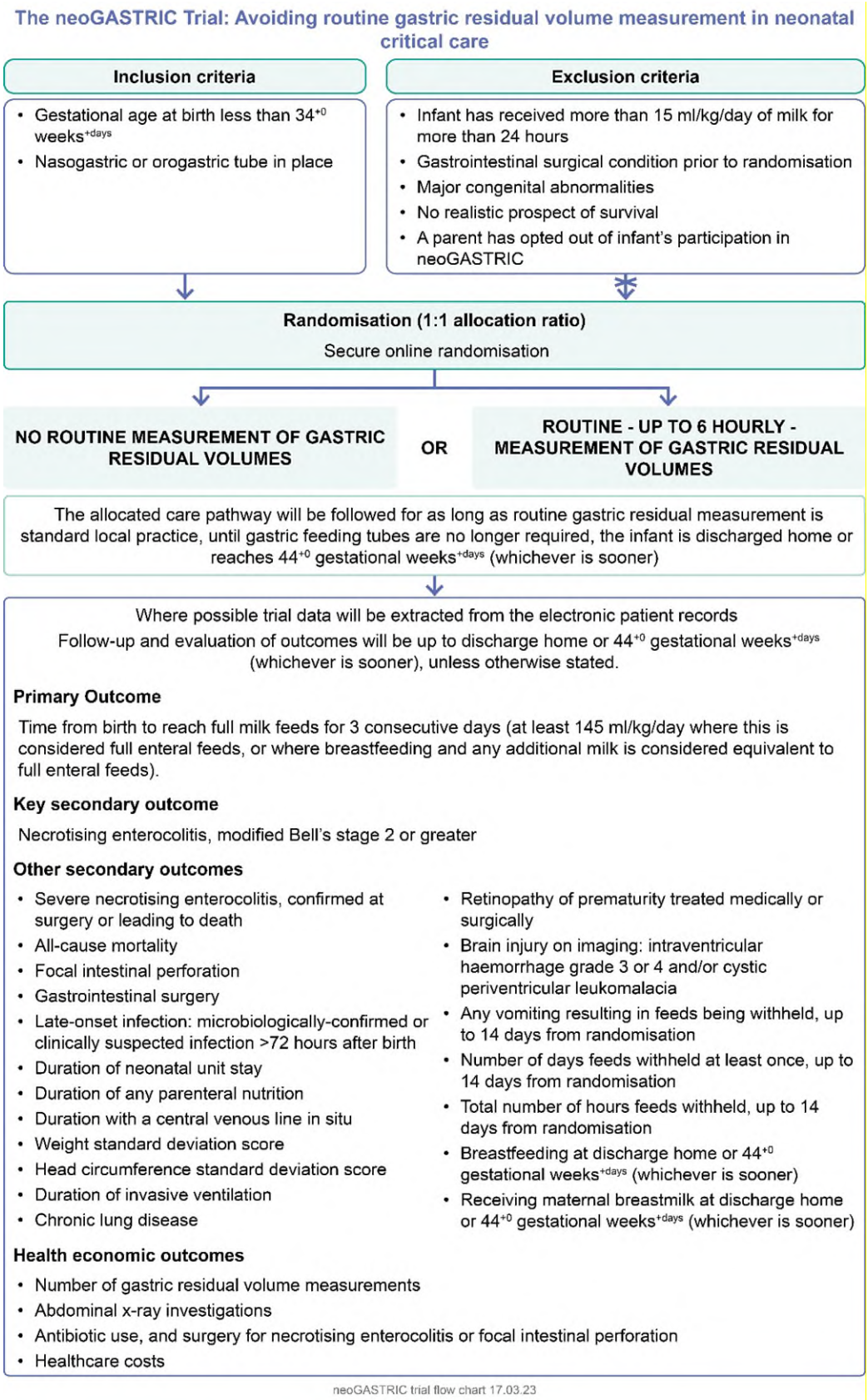
ACI	Australian Chief Investigator
AE	Adverse Event
BERC	Blinded Endpoint Review Committee
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
HREC	Human Research Ethics Committee
HTA	Health Technology Assessment
ICC	Intracluster Correlation Coefficient
ISRCTN	International Standard Randomised Controlled Trial Number
LNU	Local Neonatal Unit
NEC	Necrotising Enterocolitis
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database
NPEU	National Perinatal Epidemiology Unit
NRES	National Research Ethics Service
PI	Principal Investigator
PMG	Project Management Group
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCS	School of Clinical Sciences
SDS	Standard Deviation Score
SOP	Standard Operating Procedure
SSNAP	Support for Sick Newborns and their Parents
SWAT	Study Within A Trial
TSC	Trial Steering Committee
UK	United Kingdom
USA	United States of America

TRIAL SUMMARY

TITLE	The neoGASTRIC trial: Avoiding routine gastric residual volume measurement in neonatal critical care: a multi-centre randomised controlled trial
SHORT TITLE	The neoGASTRIC trial
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.
AIMS	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 enteral feeds without increasing harm, up until discharge home or 44^{+0} gestational $weeks^{+days}$.
POPULATION	Preterm infants (born less than 34^{+0} gestational $weeks^{+days}$) admitted to participating neonatal units in the United Kingdom and Australia.
SAMPLE SIZE	7,040 infants
ELIGIBILITY	**Inclusion criteria:** • Gestational age at birth less than 34^{+0} gestational $weeks^{+days}$ • Nasogastric or orogastric tube in place **Exclusion criteria:** • Infant has received more than 15 ml/kg/day of milk for more than 24 hours • Gastrointestinal surgical condition (including suspected necrotising enterocolitis and focal intestinal perforation) prior to randomisation • Major congenital abnormalities • No realistic prospect of survival • A parent has opted out of infant's participation in neoGASTRIC
CARE PATHWAYS TO BE COMPARED	1. No routine measurement of gastric residual volumes 2. Routine, up to 6-hourly, measurement of gastric residual volumes The allocated care pathway will be followed: • for as long as routine gastric residual volume measurement is standard local practice or, • gastric feeding tubes are no longer required or, • the infant is discharged home or, • the infant reaches 44^{+0} gestational $weeks^{+days}$
OUTCOME MEASURES	Follow-up and evaluation of outcomes will be up to discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner), unless otherwise stated. **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)

	Key secondary outcome (non-inferiority outcome) Necrotising enterocolitis, modified Bell's stage 2 or greater (1), evaluated by blinded endpoint review committee **Other secondary outcomes** (superiority outcomes) • Severe necrotising enterocolitis, confirmed at surgery or leading to death • All-cause mortality • Focal intestinal perforation • Gastrointestinal surgery • Late-onset infection: microbiologically-confirmed (2, 3) or clinically suspected infection (4) >72 hours after birth, evaluated by blinded endpoint review committee • Duration of neonatal unit stay • Duration of any parenteral nutrition • Duration with a central venous line in situ • Weight standard deviation score • Head circumference standard deviation score • Duration of invasive ventilation • Chronic lung disease • Retinopathy of prematurity treated medically or surgically • Brain injury on imaging: intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia (5) • Any vomiting resulting in feeds being withheld, up to 14 days from randomisation • Number of days feeds withheld at least once, up to 14 days from randomisation • Total number of hours feeds withheld, up to 14 days from randomisation • Breastfeeding at discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner) • Receiving maternal breastmilk at discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner)
HEALTH ECONOMICS	• Number of gastric residual volume measurements • Abdominal x-ray investigations • Antibiotic use, and surgery for NEC or focal intestinal perforation • Healthcare costs
DURATION	Total duration 50 months (including a 12 month internal pilot and a total of 36 months recruitment)

TRIAL FLOWCHART



1 INTRODUCTION

1.1 Rationale for routine measurement of gastric residual volumes

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 (6).

The use of gastric feeding tubes is standard of care for preterm infants below approximately 34 gestational weeks (7, 8, 9).

Routine measurement of gastric residual volumes is established practice in many UK and Australian neonatal units (8). The rationale underpinning this practice is to inform feeding decisions, to assess 'feed intolerance', and to predict and potentially prevent necrotising enterocolitis (NEC) (10, 11). Despite evidence that gastric aspiration inaccurately measures gastric residual fluid volume (12) and is influenced by infant position and nasogastric tube size (13), their measurement remains deeply ingrained in many centres.

1.2 Gastric residual volumes and necrotising enterocolitis

Large-volume, bilious or blood-coloured gastric aspirates – in conjunction with other signs such as abdominal distension and tenderness, shock and respiratory compromise – are commonly seen in infants with NEC. Whether regular monitoring of gastric aspirates allows prediction of NEC early enough to modify disease course and outcome is however not well-evidenced (10, 11). Despite this poor evidence, prediction of NEC is a key driver of routine measurement of gastric residual volumes in UK and Australian neonatal care (14).

1.3 Adverse effects of routine measurement of gastric residual volumes

Potential adverse effects include delayed achievement of full enteral feeds (15, 16) with consequent risk of associated complications such as late-onset infection (17, 18) and longer neonatal unit stay (19, 20), discomfort/damage to gastric mucosa which is a key concern to parents (14), and depletion of gastric secretions (21).

1.4 Evidence from randomised trials

Five small, single-centre neonatal randomised controlled trials undertaken in the USA and India have been undertaken comparing routine with no routine measurement of gastric residual volumes (15, 19, 20, 22). A systematic review and meta-analysis of these trials was underpowered to detect a difference in NEC between routine and no routine measurement groups (relative risk 0.80; 95% confidence interval 0.31 to 2.08; 421 participants), and found only low quality evidence of a difference in time to reach full feeds at 150 ml/kg/day (mean difference -3.19 days, 95% confidence interval -4.22 to -2.16 days) (16). Data from these previous trials are not generalisable to NHS or Australian care due to the trial populations and settings.

1.5 Current practice

Routine measurement of gastric residual volumes to guide feeding is widespread in the UK (8), Australia (7), the US (9) and internationally. In a national UK survey of practice (59) 62% of responding neonatal units reported measuring gastric residual volumes either before each feed or at regular intervals and at least every 6 hours, and routinely measuring in all infants that receive gastric feeds without gestational age or birthweight cut-off (8). A national survey of practice in Australia reported similar findings (7). 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.

1.6 Feasibility of a trial and clinical equipoise

Interviews and focus groups with parents and healthcare professionals found that 85% of healthcare professionals and 90% of parents supported a randomised controlled trial comparing routine measurement of gastric residual volumes with no measurement (23), and identified such a trial as important; the majority of parents would consent for their infant to be in the trial (14). Findings from the feasibility study (23) have informed this protocol including patient information materials, approach to recruitment and consent, and selection of outcomes.

1.7 Research question

Among preterm infants less than 34 weeks' gestation (Population), does not routinely measuring gastric residual volumes (Intervention), compared with routine up to 6 hourly measurement of gastric residual volumes (Comparator), lead to a reduction in time taken to get to full milk feeds without increasing harms (Outcome)?

2 TRIAL OBJECTIVES

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 $weeks^{+days}$.

2.1 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 Secondary Objectives

2.2.1 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 necrotising enterocolitis, up until discharge home or 44^{+0} gestational $weeks^{+days}$.

2.2.2 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.

3 TRIAL DESIGN

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.

3.2 Duration

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

4 PARTICIPANTS

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

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.

4.3 Setting

Neonatal units caring for preterm infants, including the following levels of neonatal units: Neonatal Intensive Care Units (NICUs), Local Neonatal Units (LNUs) and Special Care Baby Units (SCBUs) in the United Kingdom and tertiary neonatal units in Australia

4.4 Inter-Hospital Transfer

Participating neonatal units will be either:

1. A recruiting site where infants may be recruited, randomised, and commence participation in the trial;
2. A continuing care site where the allocated care pathway (no routine measurement of gastric residual volumes or routine up to 6-hourly measurement of gastric residual volumes) will continue to be followed and data collected if a participating infant is transferred in from a recruiting site before cessation of their allocated care pathway.

4.5 End of Trial

The end of trial will be defined as the date when the trial database is locked.

5 PATHWAYS OF CARE TO BE COMPARED

5.1 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:

- for as long as routine gastric residual measurement is standard local practice or,
- gastric feeding tubes are no longer required or,
- the infant is discharged home or,
- the infant reaches 44^{+0} gestational weeks^{+days}

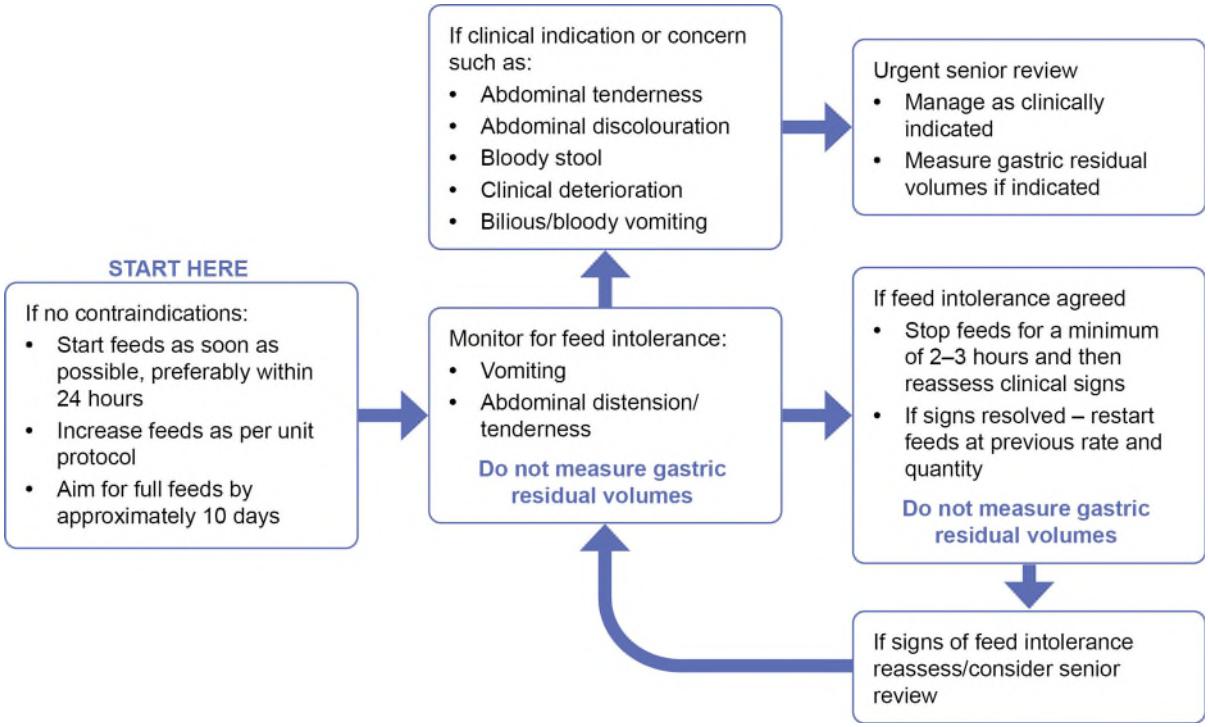
Where an infant develops a condition for which gastric residual measurement is clinically indicated – for example suspected necrotising enterocolitis or suspected gastrointestinal obstruction – such gastric residual measurement is no longer 'routine' so should be undertaken as clinically indicated in 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:

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

Within this pathway of care, feed tolerance will be assessed by monitoring the infant for symptoms such as 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 (8) and a consensus meeting (14) which involved parents, neonatologists, neonatal nurses, dieticians and trial methodologists.

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



5.1.2 Routine, up to 6-hourly, measurement of gastric residual volumes

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.

5.2 Concomitant Care

In order to ensure that this pragmatic trial is as generalisable as possible to current practice, other aspects of nutritional practice will be according to usual unit practice. This includes, but is not limited to, timing of commencement of feeds, speed of increase of enteral feeds and choice of milk where mother's milk is insufficient.

5.3 Adherence to the allocated care pathways

Adherence to the allocated care pathway will be recorded in the *Daily Feed Log* by recording the number of gastric residual volume measurements per calendar day until an infant achieves the primary outcome (full enteral feeds). Where an infant has a clinical indication or concern for assessment of gastric residual volumes (for example, suspected NEC or intestinal obstruction – see Section 5.1) these will not be considered *routine measurement of gastric residual volumes* and so will not be reported as crossover or non-adherence for this arm of the trial.

5.3.1 Non-adherence for the purpose of site monitoring

For the purpose of site monitoring if any of the following occur in one calendar day, sites will be contacted to put processes in place to improve adherence:

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

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

5.3.2 Non-adherence for the purposes of analysis and internal pilot study progression criteria

Non-adherence for the purposes of the per protocol analysis and defining *crossover from 'no routine measurement of gastric residual volume' arm* for the internal pilot study progression criteria (see Section 10), 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 Section 5.1) this will not be counted as non-adherence.

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

6 TRIAL OUTCOME MEASURES

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

Primary outcome	**Primary outcome measure**	**Time point**
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)	
Secondary outcomes	**Secondary clinical outcome measures**	**Time point(s) of evaluation**
Key secondary outcome (non-inferiority outcome)	NEC: modified Bell's stage 2 or greater (1), evaluated by blinded endpoint review committee	

Other secondary outcomes	• Severe NEC, confirmed at surgery or leading to death	
	• All-cause mortality	
	• Focal intestinal perforation	
	• Gastrointestinal surgery	
	• Late-onset infection (>72 hours after birth): microbiologically-confirmed (2, 3) or clinically suspected infection (4), evaluated by blinded endpoint review committee	
	• Duration of neonatal unit stay, in days, including all levels of care	
	• Duration of any parenteral nutrition, in days	
	• Duration with a central venous line in situ, in days	
	• Weight standard deviation score	
	• Head circumference standard deviation score	
	• Duration of invasive ventilation, in days	
	• Chronic lung disease: receiving oxygen or respiratory support at 36 weeks' corrected gestation age	
	• Retinopathy of prematurity: treated medically or surgically (24)	
	• Brain injury on imaging: intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia (5)	
	• Any vomiting resulting in feeds being withheld	Up to 14 days from randomisation
	• Number of days feeds withheld at least once	Up to 14 days from randomisation
	• Total number of hours feeds withheld	Up to 14 days from randomisation
	• Breastfeeding	At discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner)

	• Receiving maternal breastmilk	At discharge home or 44^{+0} gestational weeks^{+days} (whichever is sooner)
Health economic outcomes		
	• Number of gastric residual volume measurements†	
	• Abdominal x-ray investigations†	
	• Antibiotic use and surgery for NEC or focal intestinal perforation	
	• Healthcare costs	

† Data to inform this outcome will be recorded within the pilot study/process evaluation

6.1 Blinded Endpoint Review

Blinded endpoint review will be used for the outcomes of modified Bell's stage 2 or greater NEC, late-onset infection and, where appropriate, time to full feeds, and will be conducted in accordance with a Blinded Endpoint Review Committee (BERC) Charter, written and agreed by the PMG and TSC. Time to full feeds has been defined to be objective and will not need blinded review in the majority of cases; we will undertake blinded endpoint review where time to full feeds is not clear. The BERC reviewers will comprise neonatal healthcare professionals who are expert in the fields for which blinded endpoint review data is being collected.

7 RANDOMISATION AND ENROLMENT PROCEDURE

7.1 Screening and eligibility assessment

In UK and Australian units potential participants meeting the eligibility criteria will be identified by the neonatal team after admission.

Since the eligibility criteria do not require specific medical evaluation, assessment of eligibility is accepted to be within the scope of competency of appropriately trained and experienced neonatal doctors and nurses, as delegated by the Principal Investigator.

7.2 Consent

As both care pathways under evaluation are standard neonatal practice, neoGASTRIC will use an opt-out approach (25). Parents or carers will be informed about neoGASTRIC through posters, a leaflet and/or electronic media given when their infant is admitted to the neonatal unit. Study information will be made avaliable to parents/carers prior to randomisation. After this information is made available, infants meeting the eligibility criteria will automatically be included in the trial.

Parents will have the option to opt out if they do not want their infant randomised into the trial. They will have at least 24-48 hours to do this in almost all cases, and in many cases a lot longer (given how long it takes to start feeds >15 ml/kg/day in many neonatal units). They will also be able to opt out of the study at any point after their infant is randomised (further details around withdrawals and discontinuation of the allocated intervention are provided in Section 9). The opt-out nature of neoGASTRIC means that there will not be a signed consent form. This opt-out approach has been developed with parents and parent charities; it has been shown to be acceptable to UK Research Ethics Committees (27) and in a pilot trial across multiple UK sites (26). Opt-out consent was supported by parents of preterm infants for a trial of not routinely measuring gastric residual volumes (14)

A Study Within A Trial (SWAT) is planned to evaluate the impact of parents also receiving electronic information through a smartphone/tablet on the neonatal unit (see Section 13). Parent information materials have been co-designed with parents of preterm infants on our Parent Advisory Group and in collaboration with charities Bliss, Support for Sick Newborns and their Parents (SSNAP), National Maternity Voices and the Australian Consumer Advisory Panel. Parent materials will present information in a streamlined way as previously found to be acceptable and informative by parents (26).

Opt-out consent will cover data linkage to routinely recorded long-term outcome data (for UK trial participants this will be NNRD, Hospital Episode Statistics and the National Pupil Database; and for Australian trial participants this will be administrative hospital costing records from individual participating hospitals).

There will be no financial or material incentive or compensation to take part in this trial.

7.3 Randomisation

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 (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 Data Monitoring Committee (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 and week of gestational age at birth.

7.3.1 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 (28).

7.3.2 Allocation concealment

Infants will be randomised using an online secure central randomisation service to ensure allocation concealment.

7.4 Blinding

Because it is not possible to mask the different care pathways the allocated care pathway in the neoGASTRIC trial will be unblinded. Blinded outcome assessment will be undertaken for the key clinical outcomes necrotising enterocolitis, late-onset infection and, where appropriate, time to full feeds.

Table 1: Blinding status of individuals involved in trial

Individual	Blinding status	Comments
Parents and infant	Not blinded	Not possible due to the nature of intervention. Parents will be informed which arm of the trial they have been randomised to.
Principal Investigator and other site staff	Not blinded	Not possible due to the nature of intervention. Following randomisation, an email will be sent to the PI and/or other site staff (as agreed locally) confirming allocation.
Chief Investigator	Blinded	The Chief Investigator will remain blinded to treatment allocation overall; however this is not possible for infants recruited at Chelsea and Westminster Hospital since he is responsible for clinical care at this site, and he will not be blinded for infants where he is involved in evaluating a Serious Adverse Event (SAE).
Database programmer	Not blinded	The database programmer will be responsible for the management of the randomisation database and will also have access to unblinded datasets within the trial database.
Trial and data management staff	Not blinded	Trial and data management staff will have access to unblinded individual records within the clinical database as this is an unblinded study.
Trial statistician	Not blinded	The trial statistician will draft the statistical analysis plan before they receive the first unblinded dataset. Thereafter, the trial statistician will have access to the unblinded dataset as this is an unblinded study.

Members of the blinded endpoint review committee (BERC)	Blinded	Members of the BERC will assess the CRFs and (if necessary) anonymised medical notes.

8 ADVERSE EVENTS

An independent DMC will be established to review the study data and outcomes including safety reports of Serious Adverse Events (SAEs). The DMC will ensure the safety and wellbeing of the trial participants and, if appropriate, make recommendations to the Trial Steering Committee (TSC) regarding continuance of the study or modification of the Protocol. The TSC will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence observed in a participant, which may not have a causal relationship with the trial intervention.

8.1.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect (not relevant in this trial)

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2 Reporting Procedures

The safety reporting window for this trial will be from randomisation until the end of trial follow-up (discharge home or 44^{+0} gestational $weeks^{+days}$, whichever is sooner).

8.2.1 Recording AEs

Due to the nature of the patient population, neonates in intensive care, a high incidence of adverse events is foreseeable during their routine care and treatment. Consequently, only those adverse events identified as serious will be recorded for the trial.

8.2.2 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)
- Necrotising enterocolitis 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

8.2.3 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.

8.2.4 SAEs which require expedited reporting via SAE reporting form

Any other SAEs not detailed in Section 8.2.2 and 8.2.3 are classed as unforeseeable SAEs and must be reported.

8.2.5 Reporting Procedures for SAEs

All unforeseeable SAEs, and foreseeable SAEs described in Section 8.2.3, that are deemed causally related to the allocated pathway of care must be reported on the SAE Reporting Form to the relevant coordinating centre (UK or Australian) as soon as possible after the site becomes aware of the event being defined as serious.

Sites may use one of the following SAE reporting methods:

1. Paper forms, with instructions, will be provided with the trial documentation to enable anyone to report an SAE. The completed SAE form must be sent securely to the relevant coordinating centre (NPEU CTU for UK SAEs and Newborn Research, Monash University School of Clinical Sciences (SCS) for Australian SAEs).
2. Staff with access to the trial electronic database should complete the SAE form online. An automatic email notification to the local coordinating centre staff will be triggered for SAEs reported electronically.
3. Where the above routes are not possible, then the SAE may be reported by telephone to the local coordinating centre and the SAE form will be completed.

Follow-up SAE information should be reported as necessary by the site staff and sent back to the local coordinating centre electronically.

8.2.6 Assessment of Causality

The relationship of each adverse event to the allocated pathway of care must be determined by a medically qualified individual according to the following definitions:

- Unrelated – where an event is not considered to be related to the allocated trial pathway of care.
- Possibly – although a relationship to the allocated trial pathway of care cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the allocated trial pathway of care.
- Definitely – the allocated trial pathway of care is the most likely cause.

All SAEs labelled possibly, probably or definitely will be considered as related to the allocated pathway of care.

8.2.7 Assessment of Expectedness

An SAE that is deemed to be related to the allocated care pathway will be assessed by the CI or the Australian CI (or other appropriate delegate) to determine whether the event is expected or unexpected in terms of the current known safety profile of the allocated pathway of care.

8.2.8 Review of UK SAEs

For UK SAEs, the NPEU CTU will forward a copy of the SAE form to the Chief Investigator (CI) (or safety delegate) as soon as possible on receipt within 24 hours. The CI (or safety delegate) will assess whether the SAE was as a result of trial-related activities (related) and will determine expectedness. All related and unexpected SAEs will be submitted to the sponsor at RGIT@imperial.ac.uk and the Research Ethics Committee (REC) that gave a favourable opinion of the trial within 15 days of the CI becoming aware of the event, and also to the DMC, sponsor and the R&D offices.

8.2.9 Review of Australian SAEs

For Australian SAEs, the SAE form will be forwarded directly to the designated trial coordinator at Newborn Research, Monash University SCS, and copied to the Australian Chief Investigator (ACI – Calum Roberts) (or safety delegate) at time of submission. The ACI (or safety delegate) will assess whether the SAE was as a result of trial related activities (related) and will determine expectedness. All related and unexpected SAEs will be submitted to the Human Research Ethics Committee (HREC) that gave a favourable opinion of the trial within 15 calendar days of the ACI becoming aware of the event and also to the DMC, Australian delegated sponsorship organisation and the R&D offices.

9 ASSESSMENT AND FOLLOW-UP

Table 2: Schedule of events

	PERIOD						
	Enrolment		Treatment period				Close-out
TIMEPOINT	**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							
Routine or *no* measurement of gastric residual volumes			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 or (UK only) NNRD

[4] If baby 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

Baseline data will include age and ethnicity of the infant's mother in order to accurately report on the demographics of the groups allocated to each pathway.

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. Since continuing care sites are not applicable in Australia, for Australia only, discharge data may be collected from other health care providers outside of the recruiting hospital.

It is very unlikely that incidental findings will be identified in the neoGASTRIC trial as neonates will be cared for within a neonatal unit while they are in the trial, and there are no additional trial-specific

investigations. Any incidental findings that are identified during the course of the neoGASTRIC trial will be notified immediately to the clinical team looking after the neonate in question.

9.1 Data Collection before Discharge

The majority of trial data will be collected using electronic 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.

Site staff will have authenticated and restricted access to the OpenClinica CDMS, ensuring they are only able to see data on participants recruited at their site. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases. OpenClinica is hosted by Amazon Web Services (AWS) on servers located in the UK.

The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry will undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application, hosted on secure web servers at the Nuffield Department of Population Heath, University of Oxford (NDPH) (UK participants) or located at the recruiting site only (Australian participants), will be used to store the participant's name and any other identifiable details. Trial participants will be identified by a unique trial number, which is used to link the clinical and administrative database applications.

Electronic files, such as eCRFs and other electronic or scanned documents containing personal/sensitive information, will be stored on a restricted access (named individuals) server that can be accessed only by members of the NPEU CTU neoGASTRIC trial team with permissions to access data at specified levels, held in a secure location. The data are backed up daily. Authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network, which requires individual login name and password (changed regularly). No data are stored on individual workstations.

Archiving will follow the end of trial notification for:

UK: as detailed in NPEU Standard Operating Procedures (SOPs) for a minimum of 25 years

Australia: until the youngest participant attains the age of 33.

At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines. Electronic files will be stored on a restricted access (named individuals) server held in a secure location. In line with the NPEU CTU security policy, authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked

when unoccupied. Authorised staff will process data via a secure network which requires individual login name and password (changed regularly). No data are stored on individual workstations. The data is backed up automatically overnight to an offsite storage area accessed by authorised personnel via electronic tag and key-pad systems.

At the end of the trial, trial data for Australian infants only will be transferred securely to Monash University in Australia. This will comply with the data sharing agreement in place between the parties and as per NPEU SOPs. The University of Oxford's preferred method of secure file transfer will be used. The files uploaded must be password protected and passwords must be communicated to the recipients by a different communication to the files (e.g. telephone or text).

All paper and electronic data will be stored securely in strict compliance with current data protection regulations.

Routinely recorded clinical data held in the National Neonatal Research Database (NNRD) will be used for outcomes and descriptive data for UK trial participants.

No additional blood or tissue samples are required for this trial.

The health economic analysis will utilise trial data from UK and Australian infants and the appropriateness of pooling data from both settings in the main health economic analysis will be evaluated. Health economics teams in both countries will make use of information about days ventilated, days receiving parenteral nutrition, treatments given for necrotising enterocolitis, days and levels of inpatient care provided (intensive, high dependency, special care) and transfers between units. In the UK this data will be collected using NNRD data at discharge home or 44^{+0} gestational $weeks^{+days}$ whereas in Australia trial-specific CRFs and/or administrative hospital records will be used. We will undertake a micro-costing exercise in a small sample of infants/units in the UK to understand the resource implications of conducting gastric residual volume measurements and other key resource use not available in the NNRD and hospital notes (e.g. abdominal x-rays). The appropriateness of using the same micro-costing data collection forms in the Australian health economic analysis will be evaluated based on Australia local clinical practice and pragmatic adjustments may be made. Data for the micro-costing analysis will be obtained using direct observation as part of the process evaluation described in Section 11.

For the main study, there will be no payment or reimbursement of expenses. In the process evaluation part of the project there will be an optional part where a parent/carer will be interviewed. After the interview is complete, parents/carers will be sent a letter and a £30 Amazon voucher to thank them for their time.

Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

9.2 Withdrawal

Parents/carers can request to opt out of the trial at any point. Withdrawal from the trial will not affect their infant's ongoing clinical care. Data collected up to the point of withdrawal will be used in the trial. Withdrawals will be recorded on an eCRF and the reason detailed, if it has been provided. Parents/carers who do not wish to continue with the allocated trial pathway will be asked for permission to complete data collection – if they agree to ongoing data collection this does not constitute a withdrawal, but a discontinuation of the allocated trial pathway (as detailed in Section 9.3).

9.3 Discontinuation of the Allocated Trial Pathway

Parents/carers will have the right to request to discontinue from the allocated trial pathway. Following a discontinuation from the allocated trial pathway, the care of the infant will revert to standard care (which may be the same as the allocated pathway they were receiving). The decision to discontinue will be recorded on an eCRF and data will continue to be collected. Parents are not obliged to provide a reason but if a reason is provided this will be recorded. Discontinuation from the allocated trial pathway will not affect their infant's ongoing clinical care.

In addition, the treating clinician may discontinue the allocated trial pathway at any time, if they consider this to be in the best interest of the infant's health and wellbeing. The decision to discontinue will be recorded on an eCRF and data will continue to be collected.

10 INTERNAL PILOT STUDY

A 12-month pilot study will be undertaken in selected neonatal units to test and refine the components and processes of the study. This will include a formal process evaluation, detailed in Section 11 below.

The key progression criteria for the internal pilot are site and participant recruitment, and adherence to the no routine measurement of gastric residual volume care pathway. We will also assess adherence to the routine measurement of gastric residual volume care pathway, the recruitment rate, parental opt-out, retention of infants, acceptability of the intervention, protocol adherence, safety and completeness of data collection. It will also provide information on the resource use required to undertake gastric residual measurements. Pre-defined stop-go criteria will be considered by the TSC as a package to assess viability.

Table 3: Internal pilot study progression criteria

	Red	Amber	Green
Number of sites			
Number of sites open for recruitment	<21	21–35	≥36
% of sites open	<60%	60–99%	100%
Recruitment			
Total participants recruited	<574	574–956	≥957
% of target recruited	<60%	60–99%	100%

Adherence to the intervention†			
Crossover from the intervention	>15%	5–15%	<5%

Green: continue into the main trial; **Amber:** open new centres, identify and address site specific issues through site visits, training and newsletters, review in 6 months; **Red:** urgent detailed review of options with the TSC and funder.

† The intervention is no routine measurement of gastric residual volume. Adherence to the routine measurement of gastric residual volume pathway will also be monitored but will not form part of the formal study progression criteria.

The target sample size for the internal pilot is 957. Our recruitment assumptions anticipate that each centre will take 4 months to reach a steady state of recruitment.

11 PROCESS EVALUATION (UK ONLY)

The GASTRIC feasibility study findings showed support for the proposed trial, but also highlighted the potential risk of not measuring gastric residual volumes, including delayed diagnosis of infection and gut problems, increased risk of vomiting into lungs and causing discomfort or pain. Gastric residual volume measurement is a long-standing clinical practice and there were some concerns about trial acceptability and 'buy in', particularly amongst nursing staff. We used feasibility findings (14) to design the trial and develop training materials; we plan to evaluate their success and impact on adherence to the trial protocol in a mixed methods process evaluation during the pilot phase of the trial to inform ongoing trial conduct, processes and training.

11.1 Process evaluation aim

To evaluate pilot phase trial processes, including protocol adherence and recruitment experiences to inform the successful conduct of the ongoing neoGASTRIC trial.

11.2 Process evaluation objectives

To review, with input from parents and staff:

1. Gastric residual volume measurement processes and protocol adherence
2. Acceptability of not routinely measuring gastric residual volumes
3. Experience of recruitment and consent, clinical equipoise amongst staff
4. Staff training needs: to inform ongoing trial conduct and staff training

11.3 Process evaluation design

Mixed methods: survey (questionnaire), interviews, focus groups, site observations

11.4 Process evaluation eligibility criteria

Inclusion criteria

- Parents in neoGASTRIC trial pilot phase, including those who 'opt out'
- Site research staff involved in screening, recruiting, randomising and consenting parents

Exclusion criteria

- Parents who do not speak English (interviews only)

11.5 Process evaluation recruitment and sampling

11.5.1 Questionnaire recruitment and sampling

Sites involved in the process evaluation will be amongst the first sites to open for neoGASTRIC trial recruitment; the process evaluation will also include two SWAT intervention and SWAT comparator clusters (see Section 12).

11.5.2 Staff questionnaire/survey

We will send an email (staff survey invite email) to staff involved in the care of a sample ~20 infants (i.e. the first 20 infants eligible for the trial, including those whose parents opt out of the trial at four pilot sites) to invite them to complete an online or paper questionnaire at the end of their first shift caring for the infant. Staff members will be asked to complete a questionnaire (called staff questionnaire) for each infant for a maximum of 20 infants at each of the four pilot sites (~80 infants in total across the four sites). The aim will be to explore experiences of recruitment and opt-out consent as well as any potential adherence issues and training needs. The staff questionnaire will include a decision making assessment tool to collect data for the SWAT (see objective 3,Appendix 2). Staff will be asked to place completed paper questionnaires in a stamped self-addressed envelope and return by post to the University of Liverpool. An online version will be available if preferred by staff using Jisc or qualtric platform.

11.5.3 Parent consent and questionnaire

After being provided with the neoGASTRIC trial information leaflet and a process evaluation information leaflet, site staff will ask each parent/legal representative (mothers and fathers) of the same ~20 infants to complete a brief paper questionnaire (called parent consent and questionnaire). Staff will be asked to write the infant's trial number and date at the top of the questionnaire so parent and staff questionnaires for each infant can be matched for analysis. This will include parents who have opted out of their infant's involvement in the trial, in these cases the infant's trial number will be left blank.

Staff will ask parents to complete a consent section at the beginning of the parent consent and questionnaire to indicate they have understood the purpose of the study and agree to participate. The questionnaire will aim to explore parents' views on the trial recruitment and consent processes and any factors that may have informed decisions to opt out of the trial. At the end of the parent consent and questionnaire parents will be asked to register their interest in participating in an interview at a later date. If they wish to register interest in an interview they will be asked for their contact details (e.g. telephone and email). The parent consent and questionnaire will be placed in a stamped self-addressed envelope and returned by post to the University of Liverpool.

11.5.4 Observations

The neoGASTRIC Research Associate will conduct observations at four sites to monitor protocol adherence over 3 days (including night/weekend shifts), and collect data for the micro-costing analysis

associated with measurement of gastric residual volumes including number of abdominal x-rays taken. Selection of sites will be informed by early questionnaire and recruitment data to include sites that do and do not have protocol adherence and/or recruitment difficulties.

11.5.5 Interview recruitment and sampling (parent topic guide)

We will conduct interviews with ~15–25 parents who register interest (on the parent consent and questionnaire), based on a prepared parent topic guide. Sampling will continue until the point of information power (29), which is the point at which data addresses the study aims, sample specificity (e.g., participants' experience relevant to the study aims, and sample diversity). Based on previous studies, 15–25 interviews will be required until the point of information power. We will aim to include parents from a balance of the four pilot sites and purposively sample to include those who opt out of their infants' inclusion in the trial.

11.5.6 Interview conduct

The topic guide will be informed by questionnaire findings and aims to explore issues and potential solutions to inform the main trial including: acceptability of the intervention (or no intervention), recruitment and consent process and quality of parental decision making (see objective 3Appendix 2). The University of Liverpool team will make contact with parents/legal representatives to arrange an interview within one month of consent. The researcher will begin parent and practitioner telephone interviews by explaining the aims of the study, providing an opportunity for questions and verbally obtaining informed consent for the study. This will involve the researcher reading each aspect of the neoGASTRIC Parent Interview Consent Form to participants, including consent for audio recording and to receive a copy of the findings when the process evaluation is complete. The Research Associate will tick each box on the consent form when the participant provides verbal consent and then sign the consent form. A copy is then sent to the parent. Informed consent discussions will be audio recorded for auditing purposes.

Any distress during the interviews will be managed with care and compassion. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview at any point. Any such families will be supported in obtaining appropriate help.

After the interview is complete, parents/legal representatives will be sent a letter and a £30 Amazon voucher to thank them for their time. All parents/legal representatives who express an interest in taking part but are not selected for an interview will be contacted via telephone or email Participant thank you No participation letter) to thank them for their interest in the study.

11.5.7 Focus groups recruitment and sampling

In months 4–6 of recruitment, we will contact pilot sites via email and invite staff to take part in an online (Zoom or Microsoft Teams) focus group, which will include an outline of the purpose of the focus groups and topics to be discussed. We will aim to conduct 1–3 focus groups depending in the number of sites open and involve 6–8 participants in each group sampling for variance in staff role and sites.

11.5.8 Focus group conduct

Topic guides will be informed by questionnaires and any early parent interview findings. Informed consent will be sought individually in breakout rooms before focus groups begin using the same process as outlined above for parent interviews.

A neoGASTRIC Participant thank you letter will be posted to participants after interview and focus groups including a copy of the consent form.

11.5.7 Process evaluation data storage

Questionnaire data will be stored at the University of Liverpool in a locked cabinet in the researcher's office. Audio data, observation notes and transcripts will be stored in a password protected file on a University of Liverpool drive that will only be accessed by the process evaluation team. Audio files will be deleted once transcripts are checked and anonymised. Questionnaires, observation notes, transcripts and consent forms will be stored for up to 10 years for auditing purposes.

11.6 Process evaluation analysis

During months 7–9 of recruitment process evaluation findings will be used to inform feedback to the management team to highlight any changes needed to the protocol design/study materials or staff training for the ongoing trial. Whilst reflexive thematic analysis (30) will be informed by the constant comparison approach, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (in particular, the design of the main trial and quality of parental decision making in the SWAT). Quantitative data will be analysed using descriptive statistics as appropriate. NVivo and SPSS software packages will be used to assist the organisation and analysis of data. Data from each method will be analysed separately then synthesised through the use of constant comparative analysis (31). Analysis of qualitative and quantitative parental decision making data (SWAT objective 3) will be analysed during the process evaluation. Findings will be fed into wider SWAT data analysis when the SWAT is complete (see Section 12 below).

12 STATISTICS AND DATA ANALYSIS

12.1 Sample Size

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. From the NNRD 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(32, 33), we anticipate 30% multiple births; the intracluster correlation coefficient (ICC) for multiple birth sets will be 0.3 for time to full feeds and 0.05 for NEC.

12.1.1 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 (32, 33). 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 (34). Applying these inflation rates and assuming a 5% attrition rate to discharge, the total number of infants required is 7040 (3520 per arm).

12.1.2 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.

12.2 Data analysis

The UK and Australian infants will be analysed as one cohort.

12.2.1 Descriptive statistics

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram (35). The number and percentage of infants lost to follow-up will be reported with the reasons recorded. Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean (standard deviation [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.

12.2.2 Comparative statistics

The primary analysis will be based on a modified intention-to-treat approach; participants with outcome data will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or procedure received. The *routine up to 6-hourly measurement of gastric residual volumes* group will be used as the reference group in all analyses. For the key secondary outcome (non-inferiority outcome) analysis will be based on a per protocol approach.

For binary outcomes, risk ratios and confidence intervals will be calculated using a mixed binomial or Poisson model with a log link. Risk differences will also be calculated using a mixed binomial model with an identity link. The primary outcome and other continuous outcomes will be analysed using mixed linear regression with mean differences and confidence intervals presented, where model assumptions

are satisfied. Skewed continuous outcomes will be analysed using quantile regression models, with median differences and confidence intervals presented.

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. Analyses will also be adjusted for the randomisation minimisation factors where possible; site, week of gestation at birth and multiple birth. Both crude and adjusted effect estimates will be presented, but the primary inference will be based on the adjusted estimates. The consistency of the treatment effect on the time to full feeds and NEC by gestational age group, birth weight <10th centile for gestational age, sex and country will be assessed using the statistical test of interaction. 95% confidence intervals will be used for all pre-specified outcome comparisons including subgroup analyses.

Interim analyses of accumulating data will be reviewed by an independent Data Monitoring Committee (DMC) in accordance with a DMC Charter that will be agreed at the start of the trial.

12.3 Health economic analysis

The health economic component of the trial has been designed to be efficient (making use of existing data sources in the UK and Australia) and will not place additional burden on parents at a time of great stress. The streamlined analysis, by focusing upon resource use and costs, will provide valuable information on the cost implications of both policies being evaluated and of the potential savings that may be realised across healthcare systems if the trial demonstrates that the cessation of routine residual gastric volume measurement can safely reduce the time to achieve full feeds. A collaborative approach is proposed with the UK and Australian health economics team working jointly to provide the relevant estimates of resource use and costs in each country.

12.3.1 Aims

The integrated analysis will assess the resource use and costs associated with routine measurement and with no routine measurement of gastric residual volumes.

12.3.2 Costing analysis methodology

The analysis, conducted from a healthcare system perspective, will utilise routinely available data and hospital records review for individual infants at discharge home or 44^{+0} gestational weeks^{+days}. Key healthcare resource use captured will include the number of gastric residual measurements taken and abdominal x-rays performed (to be measured during the observation phase of the process evaluation), treatment for NEC and infections, parenteral nutrition, duration of neonatal unit stay at intensive care, high dependency care and special care levels, and hospital transfers. Regardless of whether routine measurement of gastric residual volumes could bring additional benefit or be stopped without causing harm, an accurate estimate of the resources required by this activity will be essential to inform healthcare budgeting. A micro-costing analysis of gastric residual volume measurements will be carried out in a selected number of infants and sites in the UK to understand this. A data collection form will be developed with clinical input to capture the key resource use involved in this activity from the start of the process until a decision to administer or withhold feeds is made. The questionnaire will collect

information about who performs the initial aspiration and whether additional staff support is required, equipment/disposable items involved and pH measurements results. For the UK sites, gastric residual volume measurements will be observed for a representative sample of infants across 4 centres involved in the process evaluation sub-study. The resulting resource use observations will be costed and used to calculate a mean cost per gastric residual volume measurement, which will then be used to cost each measurement recorded for each infant in the trial. For the Australian sites, pragmatic adjustments may be made based on local clinical practice.

12.3.3 Neonatal care resource use data sources

The main source of resource use data associated with neonatal care will be the NNRD in the UK and trial CRF and hospital administrative records in Australia. Resource use will be costed using unit costs from established national sources in both countries. In the UK this will include the NHS National Cost Collection (36), the Unit Costs of Health and Social Care (37), and the NHS Electronic Drug Tariff (38). In Australia this includes Enterprise Agreement for medical staff, National Hospital Cost Data Collection and Medicare Australia.

12.3.4 Statistical considerations for the health economics analysis

The final sample for the analysis of resource use and cost data will contain information from infants in the UK and Australia with infants recruited from the UK contributing a larger sample (approximately 6000). Our starting point will be to conduct a fully pooled costing (e.g. resource use pooled from both countries) (39). Given our expected large sample size, we proposed to undertake formal test of heterogeneity to evaluate the appropriateness of pooling data from both settings (40). Country-specific treatment effect and cost will also be analysed for the UK and Australia respectively.

Use and costs for each category of resources as well as total costs, will be summarised using means and standard deviations. Comparisons between trial arms will be via mean differences and 95% confidence intervals. These data will be reported alongside the trial's primary and secondary clinical outcomes in the form of a cost consequence analysis. Sensitivity analyses will assess the impact of key uncertainties in the analysis upon the base-case results. All analyses will be conducted in line with good practice guidance for health economic analyses (41).

13 MONITORING

13.1 Risk Assessment

Prior to trial commencement, the NPEU CTU will perform a risk assessment of the trial that will be reviewed at regular intervals according to its own Standard Operating Procedure. This trial is a comparison of standard treatments, which does not include a drug treatment, so does not fall under the auspices of the MHRA. Based on the assessment, this trial poses minimal risk, no greater than normal care within a neonatal intensive care unit, to either the participants or the healthcare professionals delivering the trial.

13.2 Monitoring at trial coordinating centre

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

A Data Monitoring Committee (DMC) independent of the applicants and of the Trial Steering Committee (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.

13.3 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.

14 REGULATORY ISSUES

14.1 Ethics approval

The trial will only start after gaining approval from the Health Research Authority (HRA), and a National Research Ethics Service (NRES) registered ethics committee. Additionally, NHS Trust Research and Development (R&D) Offices will review the trial for Capacity and Capability for individual trial sites. The CI, or their delegate, will submit and, where necessary, obtain approval from the REC for any protocol amendments and changes to the parent information leaflet.

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. This trial will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, relevant Data Protection regulations, the principles of GCP and other regulatory requirements as appropriate.

14.2 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the trial as registered under relevant Data Protection regulations.

Data will be pseudonymised (the individual participant data will be identified by a study participant number only) with aggregated data for publication anonymised.

14.3 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this trial.

14.4 Sponsor

Imperial College London will act as the Sponsor for this trial. Delegated responsibilities will be assigned to the NHS Trusts taking part in this trial. Newborn Research, Monash University SCS, will act as the Australian delegated sponsorship organisation, taking on delegated responsibilities for participating Australian sites.

This protocol describes the neoGASTRIC trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial.

14.5 Funding

The neoGASTRIC trial is funded by the NIHR Health Technology Assessment Programme (NIHR134216) and the NHMRC NIHR Collaborative Research Grant Scheme (NHMRC2014792). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

14.6 Audits

The trial may be subject to inspection and audit by Imperial College London under their remit as Sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

15 TRIAL MANAGEMENT

The trial and SWAT will be run by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit (CTU), a specialist perinatal CTU with extensive experience delivering large randomised trials. The NPEU CTU was involved in proposal development, and will support trial coordination, data management, quality assurance, statistical and health economic analysis and dissemination. The process evaluation will be led by the University of Liverpool team who are experienced in trials methodology including studies within trials. Monash University will lead the coordination of the Australian arm of the trial.

The trial will be supervised on a day-to-day basis by the Project Management Group (PMG). This group reports to the TSC which is responsible to the trial Sponsor. The core PMG will consist of Chris Gale (Chief Investigator), Calum Roberts (Australian Chief Investigator) and NPEU CTU staff including: CTU Director, Head of Operations, Senior Trials Manager, Head of Trials Programming and Trial Statistician. The Clinical Investigators' Group, (CIG) will meet regularly. This will comprise all members of the co-applicant group and the members of the core PMG.

The trial will be overseen by a Trial Steering Committee (TSC) consisting of an independent chair and at least two other independent members. The Chief Investigator and CTU Director will also sit on the TSC. A Data Monitoring Committee (DMC) independent of the applicants and of the TSC will review the progress of the trial as agreed and provide advice on the conduct of the trial to the TSC and (via

the TSC) to the Sponsor. The DMC will act according to its Charter, which will be agreed at its first meeting.

16 PUBLICATION POLICY

The success of the trial depends on a large number of neonatal health professionals and trials unit staff. Credit for the trial findings will be given to all who have collaborated and participated in the trial including all local coordinators and collaborators, members of the trial committees, the NPEU CTU, and trial staff.

Authorship at the head of the primary results paper will take the form [name], [name]… and [name] on behalf of the neoGASTRIC Trial Collaborative Group, where named authors form part of the writing committee. The writing will be the responsibility of the writing committee which it is anticipated will include all of the investigators. Named authors will be listed in the following order: individual responsible for completing the first draft of the paper, lead analyst, all other members of the writing committee in alphabetical order, lead supervising author. All other contributors to the trial will be listed at the end of the report, with their contribution to the trial identified. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

NIHR also require researchers to publish an account of their research project in the NIHR Journals Library, in line with funder requirements at the time of publication.

Those responsible for other publications reporting specific aspects of the trial, such as detailed microbiological outcomes, may wish to utilise a different authorship model. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the TSC.

Full details of the trial will be made available to parents of infants enrolled in the trial through the trial website: https://www.npeu.ox.ac.uk/neogastric. It will also be disseminated through charities such as Bliss and SSNAP.

17 RECORD OF CHANGES

Version Stage	Versions No	Version Date	Protocol updated & finalised by	Detail the reason(s) for the protocol update
	2.0	03/04/2023		1. Some typo corrections 2. Update to SAE section 3. Addition of new secondary outcome in line with neonatal standard outcomes 4. Addition of data archiving requirement in Australia 5. Update to Eligibility criteria to clarify based on clinical feedback

				6. Update to data collection section
	3.0	19/04/2024		1. Some typo corrections 2. Changes to Section 5 and Appendix 1 updating 'serious clinical concern' to 'clinical indication or concern' 3. Update to table in section 6 to remove 'Superiority outcomes' 4. Update to Consent description (section 7.2) for clarification 5. Updates to notes in Table 2 (section 9) for clarification 6. Update to section 9, to include discharge data collection requirements for Australia only

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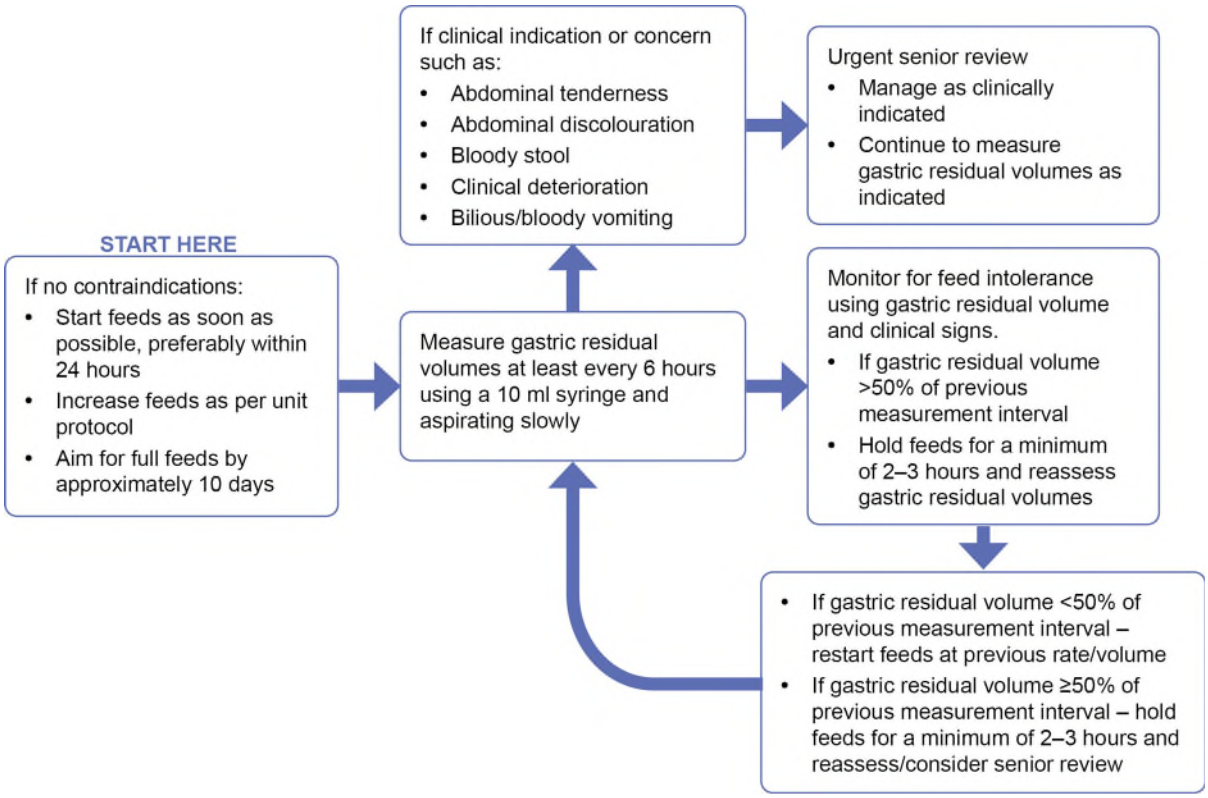
19 Appendices

Appendix 1: Suggested management within the 'Routine, up to 6 hourly, measurement of gastric residual volumes' pathway

This management algorithm represents a suggested approach for neonatal units who do not have existing guidance for the routine measurement of gastric residual volumes.

Where units have an existing pathway for routine measurement of gastric residuals which involves at least 6 hourly measurement, they can continue to use their existing pathway for infants allocated to the 'routine up to 6 hourly measurement of gastric residual volumes' pathway.



If the gastric residual volume is >50% of the previous interval feed volume (the amount of milk the infant was fed since the previous gastric residual volume check) or the residual is bloody or bilious, feeds will be held and the infant evaluated. If NEC is not suspected gastric residual volumes will be re-evaluated 2 hours later and if the aspirated residual is <50% of the previous interval feed volume, feeds restarted at the previous rate.

This pathway is based upon the most common components of current UK clinical practice (8).

Appendix 2: Study Within A Trial (SWAT) UK ONLY

Parents in neonatal units can experience high levels of stress and fear related to their infants' condition and the unfamiliar environment can exacerbate parental stress (42). Parents may be approached about participation in a research study when their newborn is critically ill, and may therefore struggle to comprehend written information, or have the capacity to make an informed consent decision (23). There is a need to explore potential alternative approaches to presenting trial information to parents (43) in the neonatal care setting, and in trials using opt-out consent, to facilitate recruitment, retention and informed decision making in neonatal trials.

SWAT Aim

To evaluate the effectiveness of presenting parents with trial information using hand-held digital multimedia and written information leaflet, compared to a standard written information leaflet, on recruitment, retention and informed decision making in the neoGASTRIC trial.

SWAT Objectives

1. To establish if parents are less likely to opt out of their infant's participation in the neoGASTRIC trial prior to randomisation if trial information is provided using hand-held multimedia, written and poster presentation compared to written and poster information alone
2. To establish if parents are less likely to opt out of their infant's participation in the neoGASTRIC trial post randomisation if trial information is provided using hand-held multimedia, written and poster presentation of information compared to written and poster information alone
3. To determine if the quality of parental decision making is affected by presentation mode.

SWAT DESIGN

A cluster randomised trial within the neoGASTRIC trial, UK centres only. Sites will be randomised at a cluster level. The SWAT randomisation will be stratified on the level of unit (LNU/SCBU and NICU).

SWAT eligibility criteria

Inclusion criteria: Parents of children eligible for inclusion in the neoGASTRIC trial

Exclusion criteria: Parents who do not speak one of the languages in which the patient information materials and video presentation are available

SWAT recruitment and sampling

neoGASTRIC sites will be randomised to either:

1. Intervention: Information leaflet, neoGASTRIC study posters and a video presentation of trial information
2. Comparator: Information leaflet and neoGASTRIC study posters

The SWAT randomisation will be stratified on the level of unit (LNU/SCBU and NICU). Sites will be randomised via a secure randomisation website (developed by a Senior Trials Programmer) accessible to the Trial Manager.

SWAT objective 3 will be addressed through parents' participation in process evaluation interviews. Please see Section 11.5 for details of recruitment and sampling and 11.6 for data analysis. Interviews will include verbal questions and an administered questionnaire to assess quality of decision making.

SWAT outcomes

Primary outcome:

- parent did not opt out of infant's participation in the trial prior to randomisation

Secondary outcomes:

- parent did not opt out of infant's participation in the trial post randomisation
- quality of parental decision making

SWAT sample size

In a cluster-randomised design, where 18 centres are randomised to the intervention and 18 centres to the comparator group, there would be 36 clusters of 277 parents (assuming a 30% incidence of multiple births). If an intra-cluster correlation coefficient of 0.05 is assumed, this would give a design effect of 15. Assuming equal-sized clusters, a background recruitment rate of 60% and two-sided 5% significance level, a cluster-randomised SWAT would have 90% power to detect a 12% absolute increase in uptake from 60% to 72% (i.e. reduction in opt-outs from 40% to 28%), and 80% power to detect a 10% absolute increase in uptake from 60% to 70% (i.e. reduction in opt-outs from 40% to 30%).

SWAT analysis

The primary analysis will be based on an intention-to-treat approach; participants with outcome data will be analysed in the SWAT groups to which they are assigned, regardless of deviation from the protocol or procedure received. The comparator group will be used as the reference group in all analyses. For the primary and secondary binary outcomes, risk ratios and confidence intervals will be calculated using a mixed binomial or Poisson model with a log link, with cluster as a random effect, and

adjusting for level of unit as a fixed effect. Risk differences will also be calculated using a mixed binomial model with an identity link.

For the analysis of the qualitative parental decision making data please refer to Section 11.6 for detail. We will use descriptive statistics to summarise the parental decision making quantitative data.