icnarc intensive care national audit & research centre

Edge Hill University

The GASTRIC-PICU Study

A randomised controlled trial of no routine gastric residual monitoring to guide enteral feeding in paediatric intensive care units.

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Chief Investigators:

Professor Lyvonne Tume and Professor Mark Peters.

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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1. Table of Contents

2. Key Trial Contacts

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3. Trial Investigators

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4. Trial Summary

Data category	Information
Scientific title	A randomised controlled trial of no routine gastric residual volume measurement to guide enteral feeding in paediatric intensive care units: the GASTRIC-PICU trial.
Public title	No routine measurement of gastric residual volume in paediatric critical care.
Primary registry and trial identifying number	ISRCTN79668198
Date of registration in primary registry	05/04/2023
Source(s) of monetary or material support	National Institute for Health and Care Research (NIHR)
Primary Sponsor	Intensive Care National Audit and Research Centre (ICNARC)
Contact for public queries	GASTRIC@icnarc.org
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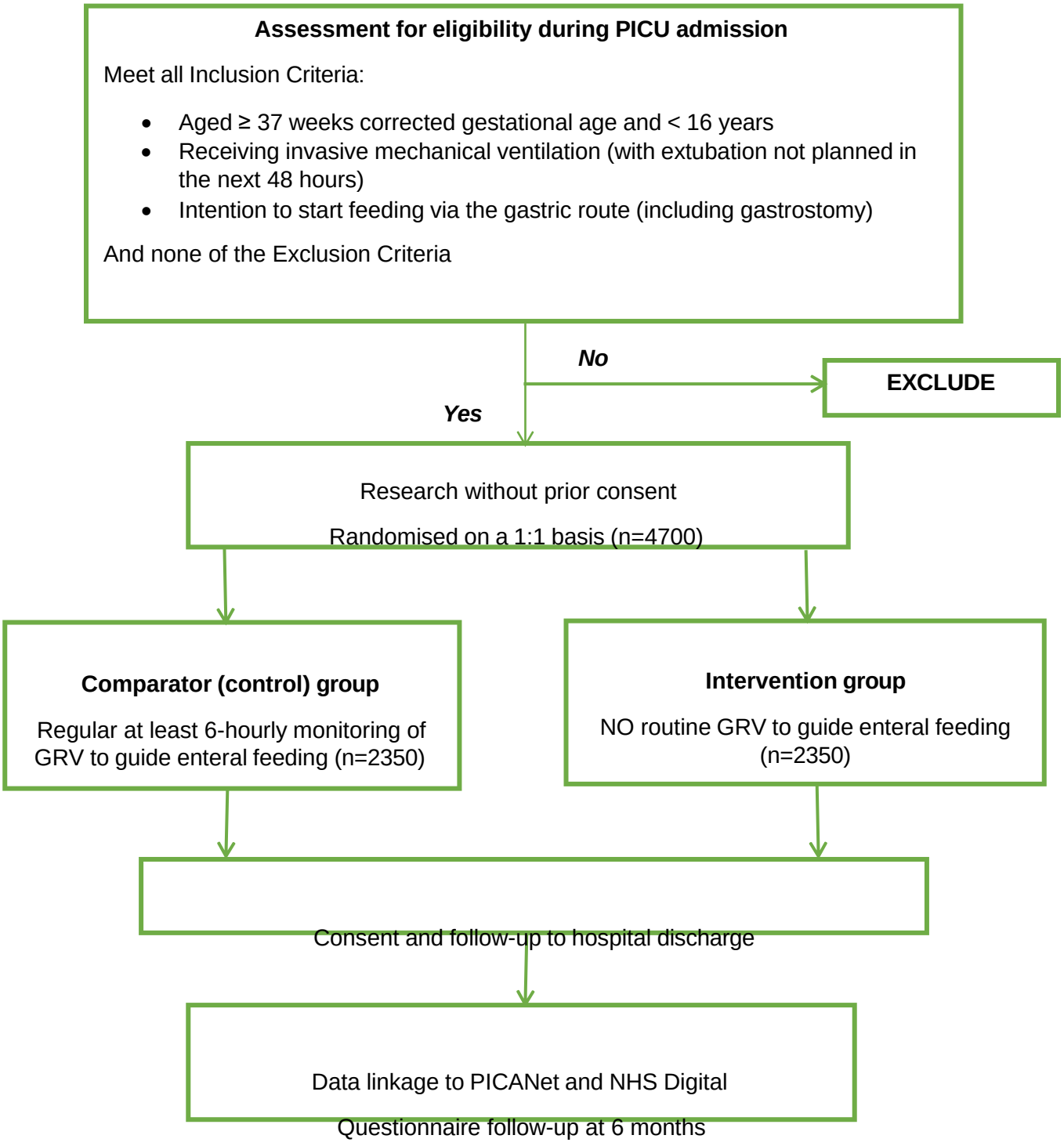
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Paediatric critical care.
Setting	19 UK Paediatric Intensive Care Units (PICUs)
Intervention(s)	The intervention is no routine measurement of gastric residual volume (GRV). Standard unit feeding protocols will be followed but without GRV measurement to guide enteral feeding. The comparator is regular at least 6 hourly measurements of gastric residual volume. Standard unit feeding protocols will be followed, and enteral feeding will be guided by at least 6 hourly gastric residual volume (GRV) measurements.
Inclusion and exclusion criteria	POPULATION Children admitted to paediatric intensive care units who are receiving invasive mechanical ventilation, enrolled within 24 hours of first meeting the below eligibility criteria: INCLUSION CRITERIA: • Aged ≥ 37 weeks corrected gestational age and < 16 years at the time of recruitment • Receiving invasive mechanical ventilation (with extubation not planned in the next 48 hours) • Intention to start feeding via the gastric route (including gastrostomy) EXCLUSION CRITERIA: • Post pyloric feeding or jejunostomy • End-of-life care plan in place with limitation of resuscitation • Children on long term mechanical ventilation • Current or recent gut pathology or surgery (e.g., necrotising enterocolitis (NEC), active GI bleeding, or any intestinal surgery)

Data category	Information
	• Known to have been enrolled in the GASTRIC-PICU trial in the last 6 months.
Study type	Multi-centre, randomised, noninferiority, open-label trial with inbuilt pilot phase (with clear stop/go progression criteria to full trial) and health economic evaluation and patient follow-up 6 months.
Date of first enrolment	May 2023
Target sample size	4,700
Primary outcomes	The two clinical co-primary outcomes are: 1) Composite outcome of survival and days free from mechanical ventilation at 30 days (non-inferiority), and 2) Percentage of the child's estimated energy requirements achieved by 72 hours after randomisation (superiority). The primary outcome of cost-effectiveness analysis is incremental net monetary benefits at six months.
Secondary outcomes	1) Time to achievement of target energy requirement 2) Time to achievement of target protein requirement 3) Diagnosis of Ventilator Associated Pneumonia (VAP) 4) Diagnosis of necrotising enterocolitis (NEC) in infants 5) Duration of time with no enteral feed in the first 7 days after randomisation 6) Incidence of vomiting leading to feed stoppage in the first 7 days after randomisation 7) Documented healthcare acquired infections 8) Length of PICU stay and hospital stay 9) Mortality at 30 days and 6 months 10) Resource use and costs 11) Health-related Quality of Life (assessed using PedsQL and CHU-9D questionnaire data) 12) Quality-Adjusted Life Years (QALYs) 13) Feeding component of the Functional Status Score
Economic outcomes	The economic analysis will also perform a cost-consequence analysis and report incremental costs alongside primary clinical outcome at 30 days.

5. Abbreviations

CEA	Cost effectiveness Analysis
CDC	Centre for Disease Control
CICU	Cardiac Intensive Care Units
CLABSI	Catheter Related Blood Stream Infections
CRF	Case Report Form
CRN	Clinical Research Network
CYAG	Children's and Young People's Group
DMEC	Data Monitoring and Ethics Committee
ECLS	Extra Corporeal Life Support
EN	Enteral Nutrition
FSS	Functional Status Score
GA	Gestational Age
GI	Gastrointestinal
GRV	Gastric Residual Volume
IRAS	Integrated Research Application System
HCAI	Healthcare Acquired Infection
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment (Funding Stream of the NIHR
INVOLVE	National advisory group that supports public involvement in health & social care research
NBM	Nil by mouth
PAG	Patient Advisory Group
PedsQL	Pediatric Quality of Life Score
PCCS	Paediatric Critical Care Society
PCCS-SG	Paediatric Critical Care Society – Study Group
PD	Peritoneal dialysis
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PIS	Participant/Parent Information Sheet
PPIE	Patient and Public Involvement and Engagement
NEC	Necrotising Enterocolitis
NICU	Neonatal Intensive Care Unit
QALYs	Quality of Life adjusted Years
SAP	Statistical Analysis Plan
SSI	Surgical Site Infections
TSC	Trial Steering Committee
UK	United Kingdom
VAP	Ventilator Associated Pneumonia

6. Trial Flowchart



7. Background and Rationale

Underfeeding and inadequate delivery of nutrition remain a problem in paediatric intensive care units (PICUs) worldwide. A large international study of children in 31 PICUs showed only 37% of children received their required energy intake (1) . On average, children in PICUs receive less than half of their predicted energy requirements (1). Inadequate energy delivery to critically ill infants and children has deleterious consequences. Inadequate nutrition has been associated with prolonged mechanical ventilation, impaired wound healing (including time to sternal closure following cardiac surgery in babies), increased healthcare acquired infections, longer PICU stays and increased mortality (1-6). Interruptions to the delivery of enteral nutrition (EN) are identified as the most significant preventable reason for inadequate energy achievement in the PICU (7, 8). These interruptions occur for several reasons, but the most common of these is feed intolerance as defined by a 'high gastric residual volume' (GRV) (7, 9). This practice of GRV measurement is routine and widespread in UK PICUs (8). GRV is obtained by aspirating the child's stomach contents via a nasogastric tube and is typically performed 4-6 hourly. However, the ability of these GRV measurements to predict feed intolerance is not established.

The rationale for GRV measurement is based on mitigating the perceived risk of pulmonary aspiration (from an overdistended stomach) in mechanically ventilated patients (10), but this risk remains unquantified and has been challenged in adults and neonates (11-14) (but not in children so far), suggesting the inaccuracy of this technique to assess feeding tolerance. A systematic review in critically ill adults did not find measuring GRV reduced the risk of Ventilator Associated Pneumonia (VAP) or aspiration (14). However, adult studies showed that not measuring GRV did significantly improve the achievement of energy goals.

20,000 children aged 0-17 years were admitted to UK PICUs between 2016-2018. Around half of these were less than one year old (15). PICU is an expensive service with the average cost per day of > £2000 (16), so any intervention that has the potential to reduce the length of time spent on organ support in PICU is beneficial both for the child and family and for the health service. Intensive care nurse workload is also an area of increased scrutiny, given nurses are the largest human cost in a PICU, therefore reducing nursing workload by removing any unnecessary practice would be beneficial. Furthermore, as 96.5% children now survive critical illness in the UK (15), ensuring the best possible outcomes is paramount. We know that nutritional deterioration *during* critical illness is frequent and intense (17) with both short- and long-term consequences. Thus, the effect of this practice may increase as PICU stay increases. This is important because the proportion of long-stay PICU patients in UK PICUs (and corresponding bed days) has increased significantly in the last 15 years (18) .

7.1 Review of Existing Evidence

Our feasibility work found that GRV (gastric residual volume) is undertaken in nearly all UK PICUs (8). Yet, despite the prevalence of this practice, the evidence for it reflecting feed tolerance is poor, and GRV has not been shown to correlate to delayed gastric emptying (19). The measurement of GRV itself has also been shown to be inaccurate and unreliable, being affected by the position of the feeding tube in the stomach, the patient position, the feeding method used, the nurses' technique of aspiration and the feeding tube and syringe sizes used (20). The most recent study (21) also showed that aspiration of the NGT to obtain GRV in critically ill children is inaccurate (using gastric ultrasound) and in 70% of cases did not empty the stomach. Furthermore, what volume constitutes an 'acceptable' level of GRV also remains unknown and based on little or no evidence, with arbitrary values being used to define this (7, 8). Despite GRV being routinely measured in nearly all UK PICUs (8), it is not a standard practice in French PICUs. We conducted an observational pilot study in 2015-2016 to compare practices and outcomes in a UK PICU which routinely measures GRV to a French PICU that does not (22). We found no significant differences in VAP or adverse events, and a trend towards more consistent achievement of target energy goals as the PICU length of stay increased. However, as this was a retrospective study with a small sample size, this limited our ability to draw robust conclusions.

In summary, a distinct lack of evidence exists to support the routine practice of GRV monitoring to guide enteral feeding in critically ill children, with both increasing preterm neonatal and adult research showing this practice is unnecessary and can worsen nutritional delivery (11-14). However, critically ill children are distinctly different to adults and preterm neonates and these data cannot be extrapolated, given the marked differences in age, size, pathology, and clinical endpoints. At least half of children admitted to PICU are less than 12 months of age (23) compared with the mean age of adults in UK ICUs of around 70 years with multiple comorbidities (24). More importantly, the incidence of VAP in adult ICU is much higher (21.3 per 1000 ventilator days) (11, 12) compared to that in PICUs at 5.6 – 9.2 per 1000 ventilator days (25). A specific study in critically ill children is therefore urgently needed to confirm the findings found in other critically ill populations.

7.2 Potential Adverse Effects of Routine Gastric Residual Volume (GRV) Measurement

- Impaired achievement of estimated energy and protein requirements, which may impact on clinical outcomes, prolong mechanical ventilation duration and length of PICU stay.
- Discomfort/damage to gastric mucosa – a key concern to parents (16).
- Depletion of gastric secretions and electrolyte disturbances where gastric residuals are frequently discarded.
- Unnecessary use of registered nurses' time.
- Increased costs related to disposables used to measure GRV.

7.3 Feasibility Work

Our team conducted the HTA-funded feasibility GASTRIC study that help inform the current commissioned call (20/128). Feeding intolerance, almost always defined by a 'high GRV' (8), is the most common reason in the decision to stop or withhold enteral nutrition (7, 9). This is a potentially modifiable factor, which could impact on nutritional delivery, clinical outcomes, and costs. With increasing evidence in adults and neonatal intensive care (11-14) it is now timely to examine the clinical and cost-effectiveness of this practice in critically ill children. The research is needed now because a high proportion of the ~20,000 children admitted to PICU in the UK annually are exposed to this procedure without any evidence of its risks and benefits. As the practice is so embedded into clinical practice, robust trial evidence is required to quantify the impact of this practice and determine whether this practice should be stopped. This has the potential to improve patient outcomes, reduce costs and save nursing time. Furthermore, if this practice is found to be unnecessary in this higher risk group of children, then this may have much broader implications and benefits for all tube-fed children. This trial is feasible now because of the track record of the Paediatric Intensive Care Society Group (PICS-SG) undertaking pragmatic clinical trials, such as FiSh (IRAS 195544), FEVER (IRAS 209931), SANDWICH (IRAS 209448), Oxy-PICU (IRAS 272768) and PRESSURE (IRAS 289545).

8. Aims, Objectives and Outcome Measures

8.1 Aim

To determine the clinical and cost-effectiveness of NO routine gastric residual volume (GRV) measurement to guide enteral feeding and to determine if it is non-inferior to standard at least 6 hourly gastric residual volume measurement in mechanically ventilated children admitted to PICU.

8.2 Objectives

Primary clinical objective is to determine whether no routine GRV measurement is non-inferior to at least 6 hourly GRV measurements to guide enteral feeding in critically ill ventilated children in PICU in terms of a composite outcome of survival and days free from mechanical ventilation (non-inferiority) and superior in terms of energy target achievement (superiority).

Primary health-economic objective is to conduct a full economic evaluation to assess the relative cost-effectiveness of these two practices.

Secondary objectives are to compare non-routine measurement with regular up to 6 hourly measurements in terms of other important patient and family centred outcomes and cost.

8.3 Outcome Measures

8.3.1 Primary Outcome Measures

The two clinical co-primary outcomes are:

- Composite outcome of survival and days free from mechanical ventilation at 30 days from randomisation (non-inferiority), and
- Percentage of the child's estimated energy requirements achieved by 72 hours after randomisation (superiority).

The primary outcome of cost-effectiveness analysis is incremental net monetary benefits at six months.

8.3.2 Secondary Outcome Measures

Secondary outcomes during PICU stay:

- Time to achievement of target energy requirement
- Time to achievement of target protein requirement
- Diagnosis of Ventilator Associated Pneumonia
- Diagnosis of necrotising enterocolitis in infants
- Duration of time with no enteral feed in the first 7 days after randomisation
- Incidence of vomiting leading to feed stoppage in the first 7 days after randomisation
- Documented healthcare acquired infections

Secondary outcomes assessed at PICU discharge:

- Length of PICU stay (days)

Longer terms secondary outcomes (post-PICU discharge):

- Mortality at 30 days and 6 months post randomisation
- Length of hospital stay
- Health-related Quality of Life (assessed using PedsQL and CHU-9D questionnaire data)
- Feeding component of the Functional Status Score

These outcomes are consistent with core outcomes recommended for PICU trials (26) and this is consistent with our feasibility work consulting with parents and clinicians.

Cost-effectiveness outcomes

- Resource use and costs
- Total costs at six months.
- Quality-Adjusted Life Years (QALYs) at six months.
- Incremental net monetary benefits calculated at £20,000 per QALY at six months associated with intervention (No routine GRV measurement) versus control (standard GRV measurement).

8.3.3 Outcome Definitions

NECROTISING ENTEROCOLITIS (NEC): as a new diagnosis after randomisation for children who are under 1 year old. The diagnosis is to be based on a combination of systemic, abdominal and/or radiological signs.

- Systemic signs - Include temperature instability, apnoea, bradycardia, raised inflammatory markers, thrombocytopenia, shock features. In NEC these are present with abdominal and or radiological signs stated below.
- Abdominal - Intestinal signs include abdominal distension, reduced or absent bowel sounds, larger than normal gastric aspirates, gastric bleeding, rectal bleeding, abdominal tenderness, or cellulitis.
- Radiological signs - The following are radiological signs of NEC and cases with these should be counted as a case of NEC: pneumatosis coli, portal gas, perforation – pneumoperitoneum (excluding air under the diaphragm associated with insertion of a PD catheter in theatre or in ICU, or accidental opening of the peritoneum during the operation).

A child who develops only mild systemic and/or abdominal-intestinal signs and is treated only with a 24-48 hour rule out course of NBM and antibiotics followed by re-starting feeds based on improvement should not be counted as a case of NEC.

If a general surgeon assesses the child and based on features from the systemic signs and abdominal signs elects to treat the child as NEC with NBM for minimum 5 days, then this case should be counted as a case of NEC.

Any child with a surgical abdomen who has a more serious picture – perforation, peritonitis, abdominal mass, is to be counted. There is no requirement for grading, however as a practical guide the following simplified classification has been suggested

- Moderate - any child meeting the criteria who does not need surgery and survives.
- Severe - a child with NEC who needs surgery and/or dies.

VENTILATOR ASSOCIATED PNEUMONIA (VAP): any new course of antibiotics prescribed for a presumed or proven VAP.

CATHETER RELATED BLOOD STREAM INFECTIONS (CLABSI): proven or suspected CLABSI leading to commencement or continuation of antimicrobials (Appendix 3).

SURGICAL SITE INFECTION (SSI): surgical site infection diagnosed within 30 days of the procedure, where the treating clinical team assesses the infection to be linked to the recent operation. A new course of antibiotics, or continuation of a current course for the clinical diagnosis of a surgical site infection. Surgical site infections also include those where a debridement or other surgical intervention is required to treat the infection.

ESTIMATED PROTEIN REQUIREMENT: 1.5g/kg (65% by 72 hours, 100% post-72 hours).

ESTIMATED ENERGY REQUIREMENT: estimated using the Schofield equation for age and gender (with no stress factors applied) (65% by 72 hours, 100% post-72 hours).

9. Trial Design and Setting

9.1 Trial Design

GASTRIC-PICU is a multi-centre, randomised, non-inferiority trial with internal pilot phase and integrated health economic evaluation.

9.2 Internal Pilot

An internal pilot will run from months 7-16 of the grant timeline and use a traffic light system to assess key progression criteria regarding site opening, recruitment, and adherence to the study protocol (25). The internal pilot will follow the same processes as the main trial; participants enrolled in the pilot will be included in the analysis of the main trial.

We will use a traffic light system to assess progression from internal pilot stage to the full trial as below:

	Red	Amber	Green
Number of sites opened	<14	14-18	≥19
Patient recruitment relative to target	<85%	≥85 and <100%	≥100%
Non-adherence	>15%	>5% and ≤15%	≤5%

Non-adherence is defined as the percentage of all randomised patients who meet either of the following criteria:

- Randomised to no routine GRV measurement and have had one or more GRV measurements taken within the first three calendar days following randomisation (except for any measurement taken in response to a recorded clinical indication)
- Randomised to routine GRV measurement and no measurement has been taken in at least one whole calendar day spent in PICU following randomisation, up to and including the third day after randomisation

If all the green criteria are met, the trial will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, we will consult the Trial Steering Committee (TSC) and we will act upon their advice to address the issues raised. If any of the red criteria are met, we will discuss urgently with the TSC and the funder and consider remedial actions, including discontinuation. An internal pilot report will be reviewed by the TSC, and any required remedial plans developed before a pilot phase report is submitted to the NIHR HTA.

9.3 Trial Setting

NHS Paediatric Intensive Care units (PICUs) in the UK.

9.4 Site Requirements

- Active participation in the Paediatric Intensive Care Audit Network for the UK and Ireland (PICANet) or be able to collect detailed data on patient interventions and outcomes
- Compliance with all responsibilities as stated in the GASTRIC-PICU Site Agreement

- Compliance with the study treatments, follow-up schedules and all requirements of the study protocol
- Compliance with the Research Governance Framework or Policy Framework for Health and Social Care Research and International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP).

9.5 Site Responsibilities

- Identify a Principal Investigator (PI) or two co-PIs to lead the GASTRIC-PICU trial.
- If possible, appoint an Associate/Sub-PI to assist with the running of the trial.
- Identify a Research Nurse (or equivalent) responsible for day-to-day local trial coordination.
- Identify doctor/nurse/dietitian champions for the GASTRIC-PICU trial in the unit.
- Agree to incorporate the GASTRIC-PICU trial into routine critical care clinical practice, including GRV monitoring/measurement, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation.
- Agree to adhere to participants randomised allocation and adhere to the trial protocol.
- Agree to aim to randomise all eligible patients and to maintain a Screening Log.
- Agree to data collection requirements.
- Check survival status at 6 months prior to follow up questionnaire/s.

9.6 Site Initiation and Activation

ICNARC Clinical Trials Unit (CTU) will ensure that the necessary documentation is in place before activating each site.

The following documentation must be in place prior to a site being activated for recruitment:

- A completed site initiation visit with adequate attendance to ensure knowledge of GASTRIC-PICU can be disseminated throughout the unit.
- All relevant institutional approvals (e.g., confirmation of capacity and capability).
- A fully signed GASTRIC-PICU Site Agreement.
- An up-to-date Delegation Log and Training Log.

Once activated, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- Adherence with the most recent approved version of the trial protocol.
- Training of relevant site staff in accordance with the trial protocol and Good Clinical Practice (GCP) requirements.
- Appropriate means to identify and randomise eligible patients into the trial.
- Timely data collection, entry and validation.
- Prompt notification of all serious adverse events (SAEs).

All local staff (i.e., PIs, local investigators, research teams) involved in the conduct of the trial must be listed and signed off on the Delegation Log, once trained, to carry out their delegated duties. The Delegation Log should be copied and sent to the GASTRIC-PICU Team at the ICNARC CTU whenever changes are made.

Staff members solely involved in the screening and randomisation of patients should be provided with trial-specific training to carry out these tasks and recorded on the Training Log (full GCP training will not be required for these staff members).

10. Participant Eligibility Criteria

To be eligible for the GASTRIC-PICU trial, patients must meet all the inclusion criteria and none of the exclusion criteria **at the point of randomisation**. Patients must be enrolled within 24 hours of first meeting the eligibility criteria.

10.1 Inclusion Criteria

- Aged ≥ 37 weeks corrected gestational age and < 16 years at the time of randomisation
- Receiving invasive mechanical ventilation (with extubation not planned in the next 48 hours)
- Intention to start feeding via the gastric route (including gastrostomy)

10.2 Exclusion Criteria

- Post pyloric feeding or jejunostomy
- End-of-life care plan in place with limitation of resuscitation
- Children on long term mechanical ventilation
- Current or recent gut pathology or surgery (e.g., necrotising enterocolitis (NEC), active GI bleeding, or any intestinal surgery)
- Known to have been enrolled in the GASTRIC-PICU trial in the last 6 months

10.3 Co-Enrolment

Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed.

The GASTRIC-PICU trial investigators will consider co-enrolment of participants onto other interventional studies where there is no possible conflict with the GASTRIC-PICU trial objectives. We will follow previous experience and existing guidelines from the Paediatric Critical Care Society (PCCS) regarding co-enrolment to other clinical trials to maximise patient involvement in research. Co-enrolment agreements will be put in place on a trial-by-trial basis.

11. Trial Procedures

11.1 Screening

Potentially eligible patients admitted (or accepted for admission) to the participating PICU will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record the reason patients are eligible but are subsequently not enrolled.

11.2 Randomisation

Randomisation must occur as soon as eligibility has been confirmed and will be carried out by the trained site staff. Patients will be randomised on a 1:1 basis to either ‘No routine measurement of gastric residual

volume' or 'Routine at least 6 hourly measurement of gastric residual volume' using a central web-based randomisation service. Allocation will be stratified by site, age on admission (<1 month, ≥1 month to <12 months, ≥12 months) and main reason for admission (cardiac vs other). The service will be available 24 hours a day, seven days a week.

The staff member who randomised the patient is responsible for informing the clinical team responsible for the patients care of the randomisation. Site teams are responsible for establishing robust procedures to ensure this information is not missed. The local site research team will be notified of the enrolment by email. Following randomisation, each participant will be assigned a unique GASTRIC-PICU trial number and the CRF should be completed by the local site research team.

11.3 Consent Procedures

Children who are eligible for GASTRIC-PICU trial will often become so during a period of life-threatening illness. This is a profoundly stressful situation for parents/guardians during which time there are ethical concerns both about the burden placed of trying to understand the trial and their ability to provide informed consent during a time of great distress. Furthermore, as starting feeds occurs within the first 6-12 hours of admission and delay in commencing feeds would not be normal care, we will start feeds once the child is randomised.

GASTRIC-PICU trial will use a deferred consent model ('research without prior consent'). Once a patient is identified as being eligible for the study (i.e., satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment will be commenced as soon as possible.

This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance (16) has been found to be acceptable to parents/guardians, as well as to clinicians, in several recent RCTs conducted in the paediatric critical care setting (8, 27-29). Findings from these studies have been incorporated into our consent procedures and will be used for training at sites.

11.3.1 Consent Prior to Hospital Discharge

Once notified of the randomisation of a patient to the study, a delegated member of the site research team will approach the parents/legal guardian to discuss the study as soon as practical and appropriate. This will usually be within 24-48 hours of randomisation, however, this will depend on the patient's condition and will be left to the discretion of the clinical team. If the patient has died or been discharged prior to their parents/legal guardians being approached, then the parents/legal guardians will be approached at a later point (please, see section 11.3.2 and 11.3.3).

Before approaching the parent/legal guardian, the research team member will discuss with the clinical staff that the patient is stable and that the timing is appropriate. If the patient's condition has not stabilised or the clinical team feel it is not an appropriate time, additional time should be allowed before approaching the parent/legal guardian. These discussions should be recorded in the patients' clinical notes.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians will be provided. The PIS will identify the title of the study and the Chief Investigator (CI) and include information about the purpose of the study, the implications of participating or not, participant confidentiality, use of personal data, data security, and the future availability of the results of the study. In addition to the PIS, and as advised by the Children and Young People's group (CYAG), parents/legal guardians will have the option to receive additional information, explaining the trial and its procedures, available on a video and accessed via scanning a QR code on the PIS.

A consent form will be provided indicating that: the information given, orally and in writing, has been read and understood, participation is voluntary and can be withdrawn at any time without consequence, and that consent is given for access to medical records for data collection. Parents/legal guardians will be given time

to read the PIS and have an opportunity to ask any questions they may have about their child's participation in the GASTRIC-PICU trial.

After the person seeking consent has checked that the PIS and Consent Form are understood, they will invite the parent/legal guardian to sign the Consent Form and will then add their own name and countersign. A copy will be given to the parent/legal guardian, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to age and the severity of illness and its impact on the mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained from children 8 years-old and over prior to hospital discharge if their condition allows. Study participants will be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate. Parents/legal guardians will be involved in this discussion. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal representatives to discuss with the participant following recovery.

If the participant is transferred to another hospital participating in the GASTRIC-PICU trial before the consent procedures are complete, then the originating research team will hand-over to the receiving hospital. If a participant is transferred to a non-participating site, the consent procedure in section 11.3.2 should be followed.

11.3.2 Discharge Prior to Consent Being Sought

In the event where a participant is discharged from hospital before consent has been sought or confirmed, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardians within five working days of hospital discharge to inform them of the participant's involvement in the study and provide more details. Following on from the call, as well as if there is no response to the call, the parents/legal guardians will be sent the covering letter for discharged patients and a copy of the PIS by post. Where possible, the letter should be signed by a clinical team member who is known to the family. The letter will explain that the participant has already been included in the study and how to opt-out. It will direct them to the information sheet for detailed information on the study and provide telephone contact details if parents/legal guardians wish to discuss the study with a member of the site research team.

The letter will not be sent if the parents/legal guardians will opt out from the trial on the call with the site team.

If no objection is received within four weeks of receipt of the letter, then the participant's data will be included in the study.

For this group of participants, the use of their confidential patient information (required for data linkage to NHS Digital and PICANet) will be conducted under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group). The justification for requesting Section 251 support is to eliminate the risk of bias from excluding information from specific subsets of the patients enrolled in the study.

11.3.3 Death Prior to Consent Being Sought

In the situation where a participant dies before consent has been sought, a site research team member will obtain information from colleagues and bereavement counsellors to establish the most appropriate research team member to notify the parents/legal guardians of the involvement in the research study. Parents/legal guardians can be given the information prior to their departure from the hospital, however, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal guardians (B-PIS) would be used.

If the parent/legal guardian is not approached prior to their departure from the hospital, then they will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the B-PIS

(version for bereaved parents/legal guardians) by four weeks after randomisation. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the B-PIS for detailed information on the study and provide telephone contact details if parents/legal guardians wish to discuss the study with a member of the site research team. The information can also be given to parents/legal guardians during follow-up appointments for bereaved parents (if conducted).

If no objection is received within four weeks of receipt of the letter, then the participant's data will be included in the study.

For this group of participants, the use of their confidential patient information (required for data linkage to NHS Digital and PICANet) will be conducted under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group). The justification for requesting Section 251 support is that not being able to include information from patients who die very soon after enrolment, will result in a bias and may make one of the trial arms appear more beneficial than it actually is, or hide any indications of harm caused.

11.3.4 Non-Consent and Withdrawal

Parents/legal guardians can refuse to give consent (non-consent) or withdraw from the GASTRIC-PICU trial at any time during the study. If a parent/legal guardian explicitly states that they no longer wish for their child to take part or to contribute further data to the study, their decision must be respected. The date of withdrawal of consent and any reason, if provided, should be recorded onto the secure data entry system. A File Note documenting the withdrawal should be created and filed in the Investigator Site File. Withdrawal of a child from the study should be recorded in their medical notes and no further data collected. All data collected up to the point of withdrawal will be retained and included in the study analysis.

In order to monitor non-consent, a minimal dataset will be collected for each parent/legal guardian approached but not consented: a) Study site; b) Date/time randomised; c) Randomised intervention (including whether started on assigned treatment or not); d) Reason not consented (if parents/legal guardians are willing to provide reason for non-consent); e) Outcome at PICU discharge.

11.3.5 Participants who turn 16 during PICU admission

This scenario is anticipated to occur infrequently, but should a participant turn 16 years of age during their PICU admission, the participant should be asked to provide their own consent (if they are assessed to have capacity). There is a specific Patient Information Sheet and Consent Form to be used in this scenario.

12. Trial Intervention

Daily nutritional goals in both intervention and control groups should be calculated based on the Schofield Equation, with the aim to achieve 65% of this target by 72 hours.

12.1 Intervention

The intervention arm is **no routine GRV measurement** to guide enteral feeding.

Patients should be monitored for signs of feed intolerance using clinical signs only: vomiting and other gastrointestinal or systemic signs but **not** by using GRV.

12.2 Comparator

The comparator (control arm) is routine (at least 6 hourly) GRV measurements to guide enteral feeding.

Patients should be monitored for feed intolerance using the GRV measurements as well as vomiting, and other gastrointestinal or systemic signs. The frequency of GRV should be as per standard local practice but should be at least 6 hourly. Further guidance can be found in Appendix 1 (Example Feeding Guidelines).

12.3 Concomitant Care

All other aspects of nutritional practice will be according to usual unit practice, including, but not limited to timing of commencement of feeds, speed of increase of enteral feeds and choice of feed.

12.4 Blinding

The GASTRIC-PICU trial is not a blinded trial, as it would not be practical to mask the different care pathways. Throughout the duration of the trial, only the trial statisticians and DMEC will see accumulating trial data by arm. Everyone else will remain blinded to this information until the final trial results are available.

12.5 Transferred Patients

If a randomised participant is transferred to another participating PICU, the new site should continue treatment according to the randomisation arm.

If a randomised participant is transferred to a non-participating PICU, then the randomising site should follow-up on the patient in order to obtain outcome data whenever possible.

12.6 End of Treatment

For both groups, trial treatment will continue until tube feeds have been discontinued during the PICU admission or until discharge from PICU, whichever is sooner. The trial treatment will apply at any point the patient requires tube feeds during their PICU admission (for example, the patient will return to their assigned treatment group in the case of failed attempt to stop tube feeding). The decision to discontinue tube feeds is at the discretion of the clinical team.

13. Trial Procedures

13.1 Summary of Data Collection

Data	Baseline	Day 3 (72 hrs)	Day 7	PICU discharge	Day 30	Hospital discharge	Month 6
Demographics	X						
Energy/protein targets	X	X					
Enteral feeding data		X	X				
Feed tolerance data (e.g. vomiting)		X	X				
Diagnosis of VAP					X		
Diagnosis of NEC					X		
Healthcare-associated infections					X		
Safety reporting		X	X	X	X		
Length of stay				X		X	
Mortality					X		X
PedsQL, CHU-9D (Quality of Life score)							X
Feeding component of the Functional Status Score	X						X
Health Services Questionnaire (HSQ)							X

13.2 Questionnaire follow-up

Each participant will be followed up with a questionnaire at 6 months post-randomisation to assess HRQoL and feeding status. Prior to the sending of questionnaire, survival status will be ascertained either through review of medical records by local research teams and/or via data-linkage with nationally held records (decedents will be logged in the trial records and the follow-up process ended).

At the 6-month time point, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a questionnaire pack by the ICNARC CTU containing the PedsQL, CHU-9D, which will include a feeding status question (from the Functional Status Score), and a Health Services Questionnaire. If a parent requests the questionnaire to be sent via post, then a pen and self-addressed stamped envelope will be provided for ease of return.

If there is no response, parents/legal guardians will be telephoned and asked to confirm whether they have received the questionnaire. If needed, they will be offered the option of either being sent another copy of the questionnaire (via email or post), or to complete the questionnaires over the telephone with a trained member of the GASTRIC-PICU trial team.

If a patient is an in-patient at a participating site at the follow-up time-point, the site research team will be asked to approach the parent/legal guardian and, if willing, conduct the questionnaire with the parents/legal guardians in hospital.

14. Safety Reporting

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs).

14.1 Definitions

Term	Definition
Adverse Event	Any untoward medical occurrence or effect in a patient participating in a trial. It does not necessarily have to have a causal relationship with the trial intervention.
Serious Adverse Event	A serious adverse event is an untoward medical occurrence that: - results in death - is life-threatening* - requires in-patient hospitalisation** or significant prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - is a congenital anomaly/birth defect - is otherwise considered medically significant by the Investigator. * "Life threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. ** "Hospitalisation", refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.
Serious Adverse Reaction	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention, based on the information provided.
Unexpected and Related Serious Adverse Event	A suspected Adverse Event related (possibly, probably, or definitely) to the trial intervention that is both unexpected (i.e., not consistent with the expected outcomes of the treatment being offered) and serious.

14.2 Assessment

The PI, or other medically qualified investigator as listed on the Delegation Log, should assess relatedness, expectedness and severity, categorised as follows:

14.2.1 Relatedness

None: there is no evidence of any causal relationship to the study treatment.

Unlikely: there is little evidence to suggest a causal relationship to the study treatment (e.g., because the event did not occur within a reasonable timeframe after administration of the trial treatment), and there is

another reasonable explanation of the event (e.g., the participant's clinical condition, other concomitant medications).

Possibly: there is some evidence to suggest a relationship to the study treatment (e.g., because the event occurred within a reasonable timeframe after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant medications).

Probably: there is probable evidence to suggest a causal relationship to the study treatment, and the influence of other factors is unlikely.

Definitely: there is clear evidence to suggest a causal relationship to the study treatment, and other possible contributing factors can be ruled out.

14.2.2 Expectedness

Expected: the event is listed as an expected event in the Appendix 2.

Unexpected: the event is not listed as an expected event in the Appendix 2.

14.2.3 Severity

None: indicates no event or complication.

Mild: complications result in only temporary harm and do not require clinical treatment.

Moderate: complications require clinical treatment but do not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitations to the patient.

Severe: complications require clinical treatment and results in significant prolongation of hospital stay and/or permanent functional limitation.

Life threatening: complications may lead to death.

Fatal: indicates that the patient died as a direct result of the complication/adverse events.

14.3 Recording and Reporting Procedures

The key safety outcomes in the GASTRIC-PICU trial are ventilator-associated pneumonia (VAP) and necrotising enterocolitis (NEC). Incidence of these events will be captured via the Case Report Forms and does not need to be reported additionally as SAEs.

Considering that all children eligible for the GASTRIC-PICU trial are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs – occurrences of SAEs will only be reported if they are considered to be possibly, probably or definitely causally related to the study (i.e., either as a consequence of measuring GRV, or not measuring GRV). Non-serious adverse events do not require reporting for trial purposes.

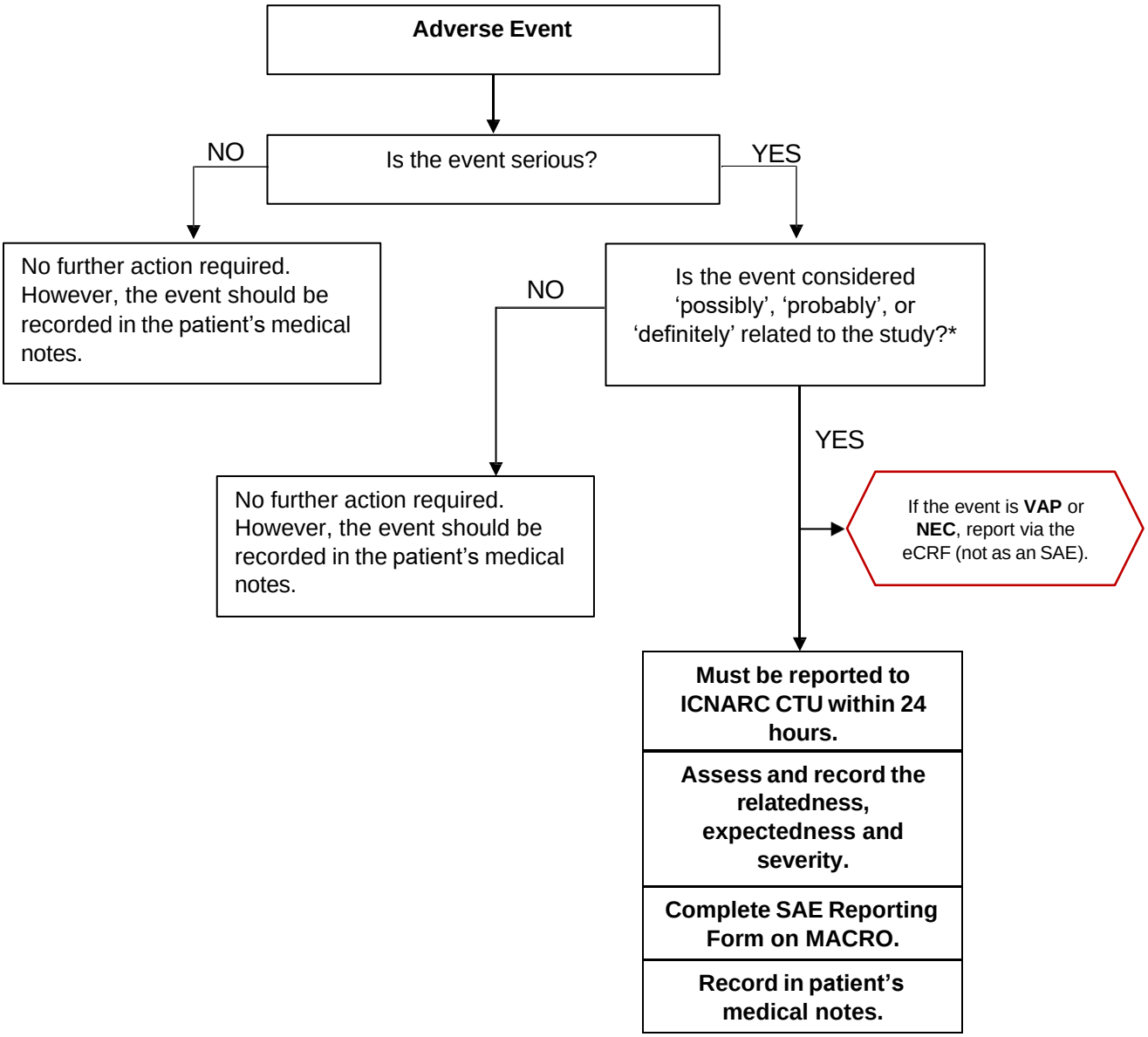
The reporting period is from the time of randomisation until 30 days post-randomisation or until final discharge from critical care unit (whichever is sooner).

All reportable SAEs (i.e., serious events which are considered possible, probably, or definitely related to the study) must be reported to ICNARC CTU within 24 hours of the site research team becoming aware of the event. Related events must be assessed for expectedness (against the list in Appendix 3). Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available.

SAEs must be recorded in the patients' medical notes and reported to the ICNARC CTU using the GASTRIC-PICU SAE Reporting eCRF. If the eCRF is unavailable, the SAE report can be sent by email to gastric@icnarc.org.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1 (Adverse Event Reporting).

Figure 1. Adverse Event Reporting



*If there is any uncertainty about whether the SAE is associated with trial treatment, then it should be reported.

On receipt of an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and consistency. Then, a clinical member of the GASTRIC-PICU Trial Management Group (TMG) will evaluate the event to determine whether it requires expedited reporting to the Research Ethics Committee (REC). If the event is a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

14.4 Notifying the Research Ethics Committee

Adverse Events that do not require expedited reporting to the REC will be reported annually to the REC. This will commence annually from the date of REC favourable ethical opinion for the trial.

14.5 Follow-Up of Serious Adverse Events

All adverse events must be followed up until resolution. The site PI(s) or other delegated investigator(s) must provide follow-up adverse events report(s) if the adverse event(s) has not been resolved at the time of the initial report submission.

15. Trial Closure

15.1 End of Trial

The end of the trial will be when the last patient has completed their 6-month follow-up, at which point the 'Declaration of end of trial' form will be submitted to the REC by the ICNARC CTU.

15.2 Archiving

At the end of the trial, the ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of five years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PIs will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of five years after the end of the study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements.

Guidance on archiving will be provided to sites in the study-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

15.3 Early Discontinuation

A single interim analysis will be performed after randomisation and 30-day follow up of 50% of the target sample size. At this analysis, the composite primary endpoint will be compared between arms and the trial will be stopped early for safety if a significant difference is seen between arms (in either direction), using a

Peto-Haybittle stopping rule of p<0.001. The co-primary outcome related to predicted energy requirements will not be evaluated at the interim analysis.

Further interim analyses will be performed if requested by the Data Monitoring and Ethics Committee (DMEC).

16. Statistics and Data Analysis

16.1 Sample Size Calculation

For the composite outcome, a non-inferiority margin of an upper limit for the odds ratio of 1.2 was selected (corresponding to a 0.8% absolute increase in mortality and a 12-hour difference in median duration of ventilation). In a survey of UK PICU clinicians this margin was preferred because it would have a meaningful impact on duration of PICU admission and it is a change that would be highly relevant to patients/families. To have 90% power to detect non-inferiority, based on the upper limit of a two-sided 95% confidence interval excluding this margin, and using an outcome distribution estimated from the SANDWICH trial (4.2% mortality and log-normal distribution for duration of ventilation with median 2.9 days and lower quartile 1.0 days) requires a total evaluable sample size of 4000. To retain power for a per-protocol analysis we have allowed for cross-over of 10% and withdrawal of 5%, to set a total target size of 4700.

The percentage of the child's predicted energy requirements achieved by 72 hours after randomisation is anticipated to be approximately normally distributed, with standard deviations within each arm between 20 and 40% (22) . The planned sample size in the intention-to-treat population will therefore provide >90% power (at P<0.05, two-sided) to detect a 4% absolute difference in energy intake based on the most conservative assumption of a standard deviation of 40%.

16.2 Internal Pilot Phase

Detailed in section 9.2.

16.3 Clinical effectiveness analysis methods

16.3.1 General principles

All analyses will be outlined in a statistical analysis plan (SAP) approved by an independent trial steering committee and seen by the independent data monitoring committee.

The following analysis populations will be defined:

- Per protocol (PP), which will exclude patients where consent to data collection has been withheld or withdrawn before day 30, and also patients classed as non-compliant as defined previously for the pilot evaluation stage.
- Intention to treat (ITT), which excludes patients where consent to data collection has been withheld or withdrawn for all data processing.
- ITT (energy intake), which excludes patients where consent to data collection has been withheld before 72 hours or withdrawn for all data processing.

16.3.2 Analysis of co-primary clinical outcomes

The composite outcome will be analysed using a proportional odds logistic regression model, with death during the first 30 days following randomisation ranked as the worst possible outcome (assigned value –1), and surviving patients assigned values according to their total calendar days free from mechanical ventilation during the first 30 calendar days following randomisation (with the day of randomisation counted as day 1). The model will be adjusted for important baseline variables including all variables used as stratification variables at randomisation. Baseline factors for inclusion in adjusted analyses will be selected a priori based on an established relationship with outcome for critically ill children, and not because of observed imbalance, significance in univariable analyses or by a stepwise selection method. The proportional odds assumption will be tested using Brant's test; however, it is noted that in the event that the proportional odds assumption is violated, the odds ratio retains an equivalent interpretation to alternative effect estimates using non-parametric, rank-based methods. The primary effect estimate will be the adjusted odds ratio, which will be calculated in both the PP and ITT populations with two-sided 95% confidence intervals. If the upper limit of the confidence interval is not more than 1.2 in both the PP and ITT populations, we will declare the intervention is non-inferior with respect to mortality and days free of ventilation by 30 days. Secondary analyses will test the same outcome for superiority/inferiority. The two separate components of the composite primary outcome will also be reported by arm.

Percentage of energy requirements met will be calculated in the ITT population, and for each patient is defined as the total calories consumed during the first 72 hours divided by the target calorie intake for the first 72 hours (capped at 100%). The primary effect estimate will be the difference in mean percentage of target achieved between the arms, which will be tested for superiority (at $P<0.05$) using a linear regression model adjusted for the same baseline variables as the analysis of the composite primary outcome. The primary effect estimate will be the difference in means, which will be reported with a two-sided 95% confidence interval.

Both co-primary outcomes will be reported in a limited number of clinically relevant subgroups, which will include patients classified by age (≤44 weeks vs >44 weeks gestational age) and reason for admission (cardiac, respiratory and other). An interaction term between subgroup and treatment arm will be added to the regression models.

A single interim analysis will be performed after randomisation and 30-day follow up of 50% of the target sample size. At this analysis, the composite primary endpoint will be compared between arms and the trial will be stopped early for safety if a significant difference is seen between arms (in either direction), using a Peto-Haybittle stopping rule of $p<0.001$. The co-primary outcome related to predicted energy requirements will not be tested at the interim analysis as evidence on energy intake alone will not be sufficient to change clinical practice.

16.3.3 Analysis of secondary clinical endpoints

All secondary clinical endpoints will be reported in both the ITT and PP populations unless otherwise specified. Data for all feeding related endpoints (time to achievement of target feeds, time to achieve protein requirement, time with no enteral feeds) will be recorded up to and including 7 days post randomisation only.

Time to event endpoints (time to achieve target feeds, time to achieve target protein requirements) will be measured from randomisation and compared between arms using adjusted Cox proportional hazards regression models. Starting on the day after randomisation, achievement of target feeds is defined as a total calorie intake for a calendar day which is equal to (or more than) the target 24-hour calorie intake for the patient. Patients who do not meet this target will be censored at death, discharge from PICU, or on day 7 following randomisation (whichever is earliest). Time to achieve target protein requirement is measured in the same way.

Binary endpoints (diagnosis of ventilator associated pneumonia, diagnosis of necrotizing enterocolitis in infants, incidence of vomiting leading to feed stoppage, documented healthcare acquired infections,

mortality at 30 days and 6 months) will be reported by arm as counts and percentages and compared using adjusted logistic regression models. Diagnosis of ventilator associated pneumonia will additionally be reported as a rate per 1,000 hours of ventilation and compared between groups using an adjusted Poisson regression model. Survival to 6 months following randomisation will also be reported using a Kaplan-Meier plot and compared between groups using an adjusted Cox proportional hazards model.

Continuous endpoints (duration of time with no enteral feed, length of stay in PICU and in hospital, PedsQL and CHU-9D) will be summarised by arm using mean and standard deviation and compared between arms using adjusted linear regression models. Feeding component of Functional Status Score will be analysed as an ordinal endpoint, summarised by the number and percentage in each category and compared between groups using an adjusted proportional odds regression model.

The end of invasive ventilation is defined as the start of the first 48-hour period when the child is free from invasive ventilation. Patients who are never liberated from invasive ventilation will be censored at the earliest of death, withdrawal of consent, transfer to a non-participating PICU (if data is unavailable after transfer), or at final database lock.

16.4 Health Economic Evaluation

A full economic evaluation will be undertaken to assess the relative cost-effectiveness of non-routine GRV measurement versus at least 6 hourly GRV measurement to guide enteral feeding in critically ill ventilated children in PICU. The CEA will take a health and personal health services perspective. The cost analysis will measure resource use associated with delivering the interventions, PICU and hospital length of stay, and follow-up visits to hospitals, primary and community care services. Resource use associated with delivering the interventions (disposables for GRV, treating NEC and feeding intolerance) will be measured from data collected in the trial case report forms (CRFs), feeding log and will be informed by expert clinical opinion. Resource use data from the PICU and hospital stay, and hospital outpatient visits will be taken from the CRFs and linked routine data from PICANet (the national clinical audit of PICUs) and NHS Digital and also through completion of the follow-up health services questionnaire (HSQ)). Use of primary care and community health services will be assessed by administering a follow-up HSQ to patients at six months. Patient-level resource use data will be valued using appropriate unit costs from the NHS payment by results and Personal Social Services Research Unit databases to calculate total costs per patient for up to six months post-randomisation. HRQoL will be measured using age appropriate PedsQL at six months. Responses from PedsQL using appropriate mapping algorithm will be mapped into preference based CHU9D score to estimate preference weighted HRQoL. HRQoL data will be combined with survival data to report QALYs. The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at six months. The economic analysis will also perform a cost-consequence analysis and report incremental costs alongside primary clinical outcome at 30 days.

16.5 Process Evaluation Survey

To evaluate the effectiveness of the processes around consent and compliance to treatment and determine if any changes are needed in the pilot phase, we will incorporate a survey of site staff midway through the pilot study. This survey will identify and explore any perceived barriers and facilitators to not measuring GRV in this trial and if the training has addressed key concerns of whether further education is required.

Sample

- PICU staff (i.e., primarily bedside nurses, but also doctors, dieticians and research nurses) and those involved in delivering the trial at sites.

Recruitment and sampling

We will send an email to pilot site staff that will describe the aims of the survey and include a link to an online questionnaire (Survey Monkey or Qualtrics platform). We will request the link is shared amongst all eligible staff with the aim to include participants (nursing and medical) from all sites open at that point in time. Due to snowball sampling, we will aim for sample variance (participants from all sites) rather than a specific sample size. Staff will be asked to complete a consent section at the beginning of the questionnaire to indicate they had understood the purpose of the study and agree to participate in the questionnaire. The short questionnaire will explore staff experiences of involvement in the GASTRIC-PICU trial, including their views on trial processes, training and anything that could be improved to inform the ongoing trial. Findings will be used to develop staff training and any potential amendments to the screening, recruitment, or consent processes (if applicable).

Analysis

Quantitative data will be analysed using descriptive statistics as appropriate. Open text responses will be analysed thematically. NVivo and SPSS software packages will be used to assist the organisation and analysis of data.

17. Data Management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper worksheets will be available to participating sites. The site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PI to qualified members of the research team, on the understanding that the site PI retains responsibility for the data collection oversight.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy, and consistency of data. Queries on incomplete, inaccurate, or inconsistent data will be sent to the local research team at participating sites for resolution. The local PI will be responsible for ensuring all queries are addressed and for overall quality of their site data.

Security of the electronic data entry system is maintained through usernames and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018.

17.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These may include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

17.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, ICNARC and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

17.3 Data Linkage

To maximise the efficiency of the design, data collection for the GASTRIC-PICU trial will be nested within the routine data collection for the PICANet audit. Data from PICANet used in the trial analysis will include:

- baseline demographics and risk factors, including the Paediatric Index of Mortality score;
- secondary outcomes of PICU mortality, duration of PICU and acute hospital stay; and
- critical care daily interventions (and associated costs), based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

All patients recruited to the trial will be informed regarding data linkage with other routine data sources. Data obtained from routine data sources will include:

- date of death for deaths occurring after discharge from acute hospital, by data linkage with death registrations (NHS Digital/Digital Health and Care Wales); and
- hospital costs for subsequent hospitalisations, by data linkage with Hospital Episode Statistics (NHS Digital) and Patient Episodes Data (Digital Health and Care Wales).

18. Trial Management and Oversight

18.1 Good Research Practice

The GASTRIC-PICU trial will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice: Principles and Guidelines based on the principles of the International Conference on Harmonisation guidelines on Good Clinical Practice. The ICNARC CTU has developed its own policies and procedures, based on these guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

18.2 Risk Assessment

Prior to trial commencement, ICNARC performed 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 PICU, to either the participants or the health care professionals delivering the trial.

18.3 Patient and Public Involvement (PPI)

There is one PPI representative as a co-investigator on the GASTRIC-PICU trial and who has been involved in its development. As a member of the Trial Management Group (TMG), they are fully involved in the work planned as part of this trial. In addition, independent PPI representative(s) will be sought for membership of the Trial Steering Committee (TSC). A Patient Advisory Group (PAG) has also been set up for the trial.

19. Monitoring, Audit and Inspection

19.1 Central Monitoring

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

19.2 On-Site Monitoring

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. Monitoring will be conducted on a risk-based approach (guided by the trial Risk Assessment).

19.3 Audit

The trial may be subject to inspection and audit by ICNARC 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.

19.4 Trial Committees

19.4.1 Trial Management Group (TMG)

The TMG comprises the GASTRIC-PICU Investigators and will be led by Chief Investigator, Professor Lyvonne Tume. Meeting of the TMG will be held quarterly, or more frequently during key stages of the trial, to ensure effective communication.

The day-to-day trial team will be led by the Trial Manager and comprise the Chief Investigator, Clinical Trials Unit co-investigators alongside the Trial Statistician, Research Assistants and Data Manager. The day-to-day trial team will meet regularly to discuss and monitor progress.

19.4.2 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e., consist of 75% independent members – including the Chair). The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards set out in the UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC will comprise of the Chief Investigator, a senior representative from the ICNARC CTU and independent members (including independent PPI representatives). Representatives from the Sponsor and Funder will be invited to observe TSC meetings which will be scheduled to take place at the following time points: (1) prior to the start of the trial; (2) following the internal pilot stage; (3-5) during the trial recruitment period; and (6) at the end of primary analysis.

19.4.3 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set up to monitor recruitment and retention, protocol adherence (including adherence to treatment protocols) and patient safety and will review the interim analysis.

20. Ethical and Regulatory Considerations

The trial will only start after gaining approval from the Health Research Authority (HRA), and a Research Ethics Committee (REC). 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 patient information materials.

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.

Confidentiality

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

Limited patient identifiable data points will be required, to enable linkage to NHS Digital (Civil Registrations and Hospital Episode Statistics datasets) and PICANet (described in section 17.3). Consent will be obtained via the parent/legal guardian before collecting these data items. If informed consent cannot be obtained (i.e., participants who are discharged or die before consent is given by the parent/legal guardian), we will collect this data under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group). Identifiable information will not be retained for the analysis.

Indemnity

ICNARC holds negligent harm and non-negligent harm insurance policies which apply to this trial.

Sponsor

ICNARC will act as the Sponsor for this trial. Delegated responsibilities will be assigned to the NHS Trusts taking part in this trial.

This protocol describes the GASTRIC-PICU 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.

Funding

The GASTRIC-PICU trial is funded by the NIHR Health Technology Assessment (HTA) Programme (NIHR133835).

21. Dissemination

The results of the GASTRIC-PICU trial will be disseminated actively and extensively. This will cover both progress during the trial period and the results at the end of the study. The outputs for the GASTRIC-PICU trial will include, but will not be limited to, the following areas:

- meeting and conference presentations (national and international) of study progress and results
- publication of study results (1) primary results and (2) longer-term outcomes, including economic evaluation; and
- incorporation into clinical guidelines.

These separate outputs will be targeted at relevant stakeholders in formats suitable for the target audience. This will ensure that the potential benefit of GASTRIC-PICU is maximised.

Following publication, the results will also be disseminated using social media for both professionals and a lay summary that will be co-designed with the Patient Advisory Group (PAG). Dissemination will also be via UK, European and International PICU networks at meetings and special dissemination events.

22. Protocol Version History

Amendment Number	Protocol Version	Protocol Date	Author(s)	Detail of Changes
N/A	V1.0	13/12/2022	GASTRIC-PICU TMG	N/A
	V1.1	06/02/2023	GASTRIC-PICU TMG	Minor changes to the protocol including clarifying wording, adding correcting typos and tidying up certain sections.
N/A	V1.2	24/02/2023	GASTRIC-PICU TMG	Minor changes to correct inconsistencies in primary and secondary outcomes, randomisation strata and to correct typos.
N/A	V2.0	21/04/2023	GASTRIC-PICU TMG	To add registration details, amend recruitment start date, study public title and add a minor change to consent section.

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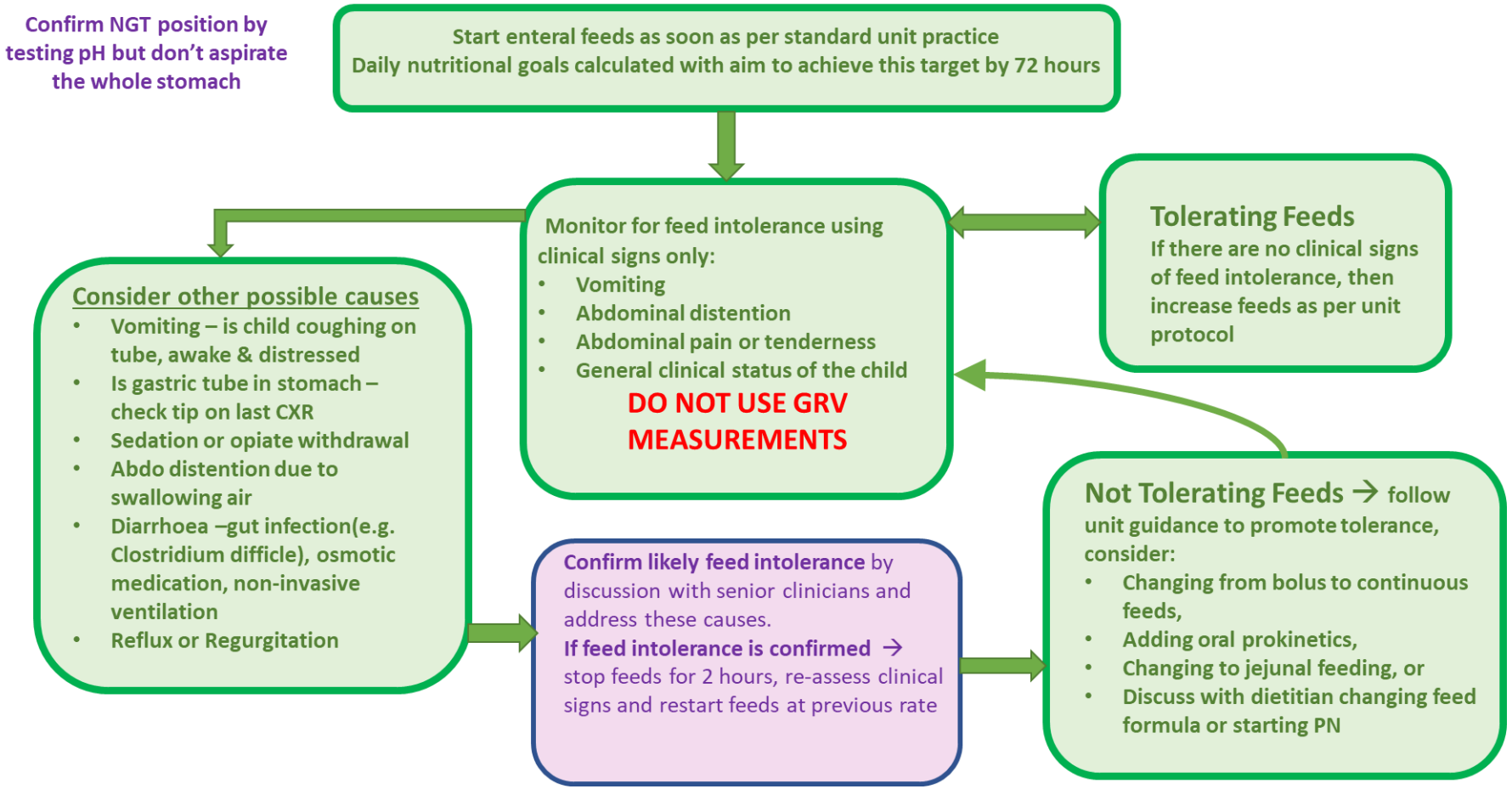
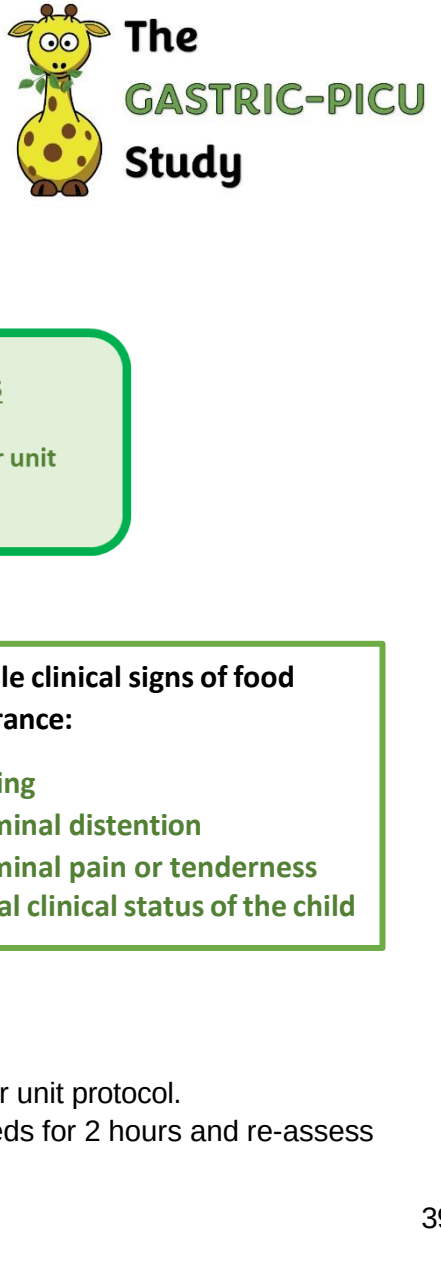
Appendix 1: Example Feeding Guidelines

Example feeding guidelines for each study arm are shown below (8):

Intervention arm flowchart (No GRV measurements to guide enteral feeding)



Control arm flowchart (Regular GRV measurements to guide enteral feeding – follow usual unit guidelines, suggested guide below)



- Feed intolerance defined as GRV > 5mls/kg or >250ml in children >40kg.
- If GRV is <5mls/kg, or <250ml in children >40kg, replace aspirate and continue to increase feeds (rate/volume) as per unit protocol.
- If GRV is >5mls/kg, or >250ml in children >40kg replace aspirate (unless faecal, bloody, or very bilious), withhold feeds for 2 hours and re-assess GRV.

Appendix 2: Expected Adverse Events

The following events will be considered expected for the purposes of trial safety reporting:

- Necrotising enterocolitis
- Pulmonary aspiration / ventilator-associated pneumonia
- Vomiting

Appendix 3: CLABSI Definition

Definition of Central Line-Associated Bloodstream Infections (CLABSI):

Criteria for a Blood Stream Infection (BSI)

- Paediatric patients
  Meets one of the following criteria:
  A: A recognised pathogen from at least one blood culture, or
  B: A common skin microorganism from 2 blood cultures drawn on separate occasions and taken within a 48-hour period
  AND
  The child has at least TWO symptoms of paediatric SIRS at least one of which must be abnormal temperature or leucocyte count:
  - ✓ Tachycardia or in infants < 1 year bradycardia
  - ✓ temperature >38.5 or <36 degrees Celsius
  - ✓ elevated respiratory rate
  - ✓ leucocyte count elevated or depressed for age that is not secondary to chemotherapy induced leucopenia

- Neonatal patients (neonates < 28 days)
  Meets one of the following criteria:
  A: A recognised pathogen from at least one blood culture, or
  B: A common skin microorganism is cultured from blood
  AND
  The infant has ONE of the following:
  - ✓ C-reactive protein >20 mg/l
  - ✓ Immature:total neutrophil ratio >0.2
  - ✓ WCC <5
  - ✓ Platelets <100

  AND_____At least two of:

  - ✓ Temperature >38 or <36.5 or temperature instability
  - ✓ Tachycardia or bradycardia
  - ✓ Apnoea
  - ✓ Prolonged capillary refill time
  - ✓ Metabolic acidosis (PH <7.35 with base deficit greater than 5)
  - ✓ Hyperglycemia (serum glucose > 12 mmol/litre on two consecutive values)
  - ✓ Other signs of BSI e.g. apathy

Diagnosis of a central line associated blood stream infection – CLABSI

The child meets all of the following criteria:

One of the criteria for blood stream infection (BSI)

AND

The presence of at least one central venous catheter at the time of the positive blood culture or a CVC that was removed within the 48 hours before the positive blood culture

AND

The signs and symptoms and the positive laboratory result including the pathogen cultured from the blood are not primarily related to infection at another site.

Central Venous Catheter (CVC)

A vascular catheter that ends close to or in the great vessels (femoral, subclavian, jugular etc). This includes peripherally inserted central catheters. CVC's may be short or long term. Common names are PICC, CVC, Portacath, hickman, broviac, lederflex etc.