A Feasibility Study of no routine Gastric residual volume measurement in mechanically ventilated Infants and Children: **the GASTRIC study**

Study Sponsor:	**University Hospitals Bristol (UHB) NHS Foundation Trust**
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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 framework and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs) and other regulatory requirements as amended.

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 publically 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.

For and on behalf of the Sponsor:

Signature:

Date:

1 March 2018

Name (please print):

Diana Benton

Position: Director R&D

Chief Investigator:

Signature:

Date:

1 march 2018

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Parent 4	TBA	

Abbreviations

AE	Adverse event
aNGT	Adapted nominal group technique
BAPM	British Association of Perinatal Medicine
BDA	British Dietetic Society
BLISS	Neonatal parent charity for preterm infants
COIN	Council of International Neonatal Nurses
CRF	Case report form
CTU	Clinical Trials Unit
EN	Enteral Nutrition
ESPNIC	European Society of Pediatric and Neonatal Intensive Care
ESPR	European Society of Pediatric Research
GCP	Good Clinical Practice
GRV	Gastric Residual Volume
HCPs	Healthcare Professionals
HQIP	Health Quality Improvement Program
HRA	Health Research Authority Health Research Authority Confidential Advisory group
HTA	Health Technology Assessment
ISOC	Independent Study oversight committee
jENS	Joint European Neonatal Societies
NEC	Necrotising enterocolitis
NIHR	National Institute for Health Research
NGT	Naso-gastric tube
NHS	National Health Service
NHS HRA CAG	National Health Service Health Research Authority Confidential Advisory Group

NICU	Neonatal Intensive care unit
NNRD	National Neonatal Research Database
NNU	National Neonatal Units
PICANet	Paediatric Intensive Care Audit Network
PICS	Paediatric Intensive Care Society
PICU	Paediatric intensive care unit
PIM2	Paediatric Index of Mortality version 2
PIS	Participant Information Sheet
PN	Parenteral Nutrition
PPI	Patient and Public Involvement
RCPCH	Royal College of Pediatrics and Child Health
RCT	Randomised clinical trial
REC	Research Ethics Committee
SMG	Study Management Group
SOP	Standard Operating Procedure
UK	United Kingdom
UKNC	United Kingdom Neonatal Collaborative
VAP	Ventilator Associated Pneumonia
WFPICS	World Federation of Pediatric Intensive care Societies

Protocol Summary

Title:	A Feasibility Study of routine Gastric residual volume measurement in mechanically ventilated Infants and Children
Short Title/acronym	GASTRIC Feasibility Study
IRAS number	244006
REC number	Not for REC review, HRA only. University Ethics Approval number
Sponsor name & reference	UHB
Funder name & reference	NIHR HTA (16/94/02)
ISRCTN no	ISRCTN42110505
Design	Mixed methods study
Overall aim	To determine if a study of not measuring GRV routinely is feasible in UK PICUs and NNUs
Anticipated study duration	18 months

Background

Underfeeding and inadequate nutrition remain constant concerns in neonatal (NNUs) and paediatric intensive care units (PICUs). An international study of 800 children in 31 PICUs showed only 37% of children received their prescribed energy intake, and that it took nearly 12 days to achieve 90% of their calorie target [1]. On average, children in PICUs receive less than half of their predicted energy requirements [2,3]. Achieving adequate nutrition in preterm infants is vital but equally challenging for different reasons. Whilst extremely preterm infants are routinely commenced on parenteral nutrition (PN) to meet their energy, carbohydrate, protein and lipid requirements, this comes with risks. PN requires invasive intravenous catheters and PN is the ideal medium for bacterial growth - the longer the PN duration, the higher the risk of developing severe infections [4,5]. UK data shows that for babies born at 24 weeks, the median time taken to establish enteral feeding is 19 days (NNRD 2017). Delays in starting and establishing adequate nutrition via the enteral route are known to increase the risk of infectious complications and possibly death [6,7]. Interventions to safely reduce the time to full enteral feeds therefore offer significant health and economic benefits and savings from reduced reliance on costly intravenous feeding.

Inadequate energy delivery to critically ill infants and children has deleterious consequences. There is evidence that malnutrition is prevalent in mechanically ventilated children on admission to PICUs worldwide [8] and that this is linked to worse patient outcomes [9,10], and longer length of mechanical ventilation and intensive care stay [11-14]. There is also evidence in preterm infants that neonatal nutritional status can affect outcomes; negative effects on brain development is an especially worrying consequence of inadequate nutrition [15-17]. A common nursing practice to assess enteral nutrition (EN) 'tolerance' is to measure gastric residual volume (GRV) frequently and routinely [18-21]. GRV is known to be a significant factor in the decision to stop or withhold enteral nutrition [21-24]. Indeed, 'high' GRV often leads to withholding EN and this is a common barrier to delivering adequate amounts of EN in NNUs and PICUs, [22-25].

Despite the prevalence of this practice, the evidence for GRV actually reflecting feed tolerance is poor, and GRV does not correlate directly to enteral feeding tolerance [26-30]. GRV is frequently inaccurate due to position of the feeding tube in the stomach, patient position, feeding method, technique of aspiration and tube and syringe sizes used. What volume constitutes an 'acceptable' level of GRV also remains unknown. So, not only is GRV unreliable as a procedure, but it is also a

time consuming, taking up valuable nursing time and resources (increasing costs) which may be best spent on other patient related tasks [30].

The practice of GRV measurement is widespread in PICUs and NNUs internationally [18,20,21], but with increasing evidence questioning the practice it is now timely to examine this practice in critically ill neonates and children. The measurement of GRV features heavily in efforts to mitigate the perceived risk of pulmonary aspiration in mechanically ventilated patients [26], this risk remains unquantified [32]. In adult intensive care trials, accepting a higher GRV (500ml compared to 200ml)[33] or not measuring GRV at all [32,34] did not adversely affect patient outcomes of ventilator associated pneumonia(VAP) or gastrointestinal complications, however did it improve the achievement of energy goals. A further study showed that just by measuring GRV the risk of delivering inadequate energy increased by 38%.[35]. A before and after study showed that not measuring GRV in 233 preterm infants <34 weeks gestation, resulted in a shorter time to achievement of full enteral feeds with no greater incidence of NEC [36]. So, increasingly, this routine practice is being challenged in NICU, PICUs and across critical care generally [37,38,39]. Despite GRV being routinely measured in all UK and Irish PICUs [18] it is not standard practice, in many French PICUs and NNUs. Our team conducted a pilot study conducted in 2015-2016 to compare practices and outcomes in a UK PICU which routinely measures GRV to a French PICU that does not. We found no significant difference in VAP or adverse events, and a trend towards more consistent achievement of target caloric goals as PICU length of stay increased [38]. In conclusion, a distinct lack of evidence exists to support the traditional, time-consuming routine GRV monitoring as part of enteral feeding protocols in both infants and children. Therefore, there is an urgent need to determine whether it is possible to conduct a trial of routine GRV measurement compared to no GRV in critically ill infants and children.

Aims and objectives

The GASTRIC feasibility study will meet the commissioning brief by the HTA, to answer the question: Is it feasible to conduct a study identifying the impact of not measuring gastric residual volume on clinical outcomes in mechanically ventilated infants and children receiving enteral feeding? To achieve this our specific study objectives are to:

1. Undertake a literature review to identify key outcome measures used for trials of enteral feeding in the PICU and NICU population

2. To establish 'standard care practices' around enteral feeding and GRV measurement in all UK PICUs and NNUs (via an e-survey)

3. To explore healthcare professionals (nurses, doctors and dietitians) views around GRV measurement, acceptability of not measuring GRV, alternative methods to assess feed tolerance, willingness to randomise to or comply with a future trial, barriers to recruitment, perceived training needs and inclusion and exclusion criteria

4. To explore PICU and NICU parents and/or patients views around GRV measurement, acceptability of not measuring GRV, willingness to agree to a future trial, barriers to recruitment, patient (parent) centred outcomes and information needs for parents

5. To determine and gain consensus on future trial issues including optimal trial design, primary and secondary outcome measures and inclusion and exclusion criteria.

6. To determine trial feasibility (in both PICU and NICU) using routinely collected national clinical data sets (PICANet and NNRD) and inform sample size calculations for a future trial.

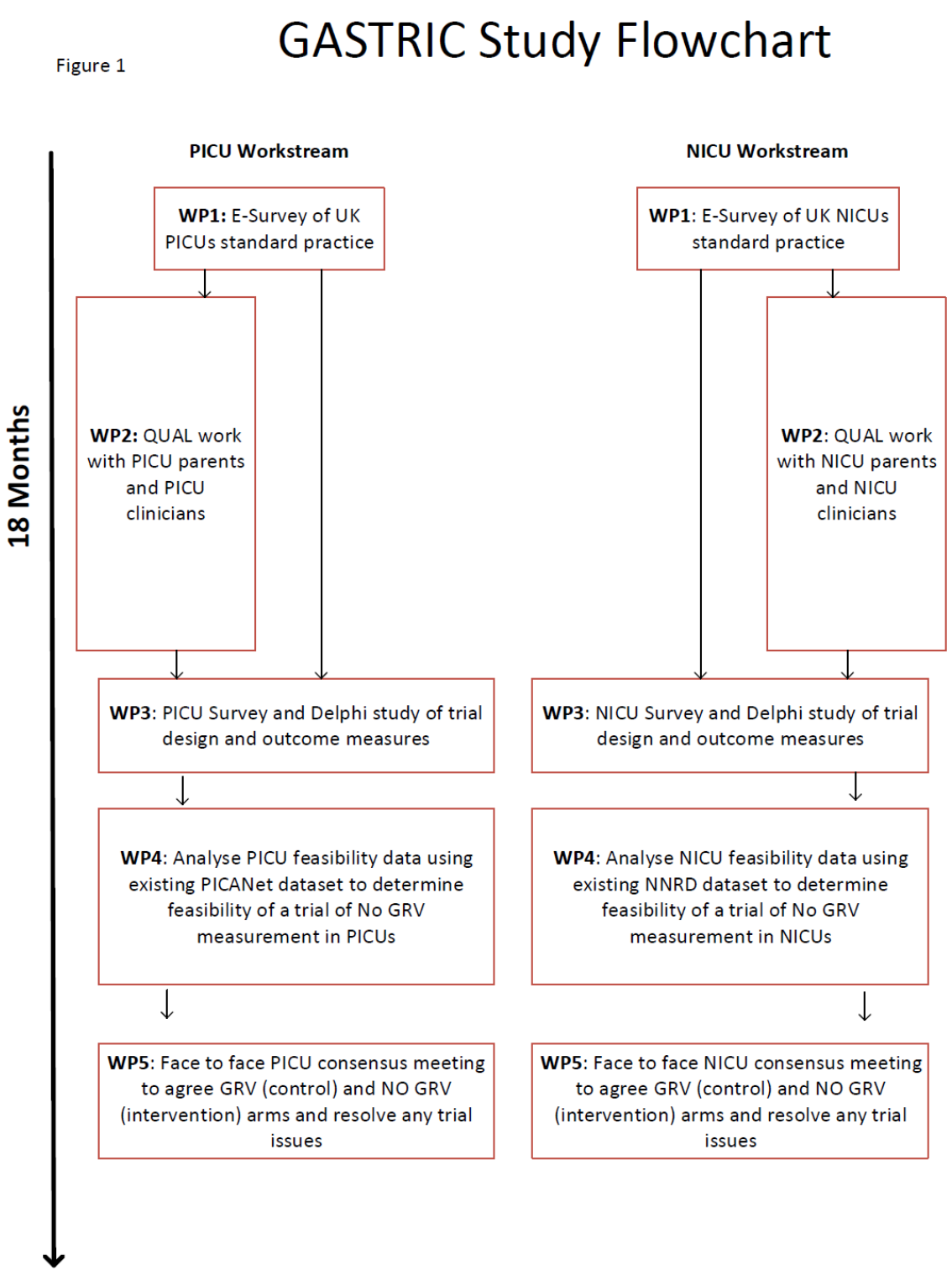
7. To agree (using a consensus process) a standard (control) arm (with routine GRV measurement) and an intervention arm (no routine GRV measurement) of a future trial.

8. To integrate all the data generated and achieve the aim of the feasibility study to determine whether a trial of no GRV measurement is feasible in UK PICUs and NNUs

Study design

A mixed method study involving 5 linked work packages, running in two parallel arms, one in NICU and one in PICU (See Study Flowchart) over an 18-month time frame (below Figure 1).

Figure 1



Target population: PICU and NICU clinicians (nurses, doctors, and dietitians), trialists and PICU and NICU parents and/or past patients if appropriate.

Setting/context: 190 NNUs and 27 PICUs across the UK

Sampling and data collection:

A literature review of all studies (adult, neonates and children) involving GRV measurement as an intervention in critically ill patients was completed in January 2018. It has critically appraised and summarised detailed data relating to study designs, inclusion and exclusion criteria used, primary and secondary outcome measures used are summarised separately for PICU and NICU. This information will provide important background information for the e-Delphi study, which aims to achieve consensus on trial issues.

Work Package 1 – Surveys to establish standard practice

Work package 1 will involve an electronic survey to all UK PICUs and NNUs to establish 'standard care practices' around enteral feeding and GRV measurement. We will conduct this through our national research networks, thus our sample size is 27 UK PICUs [Paediatric Intensive Care Audit Network, PICANet 2016] and 190 NNUs [National Neonatal Research Database NNRD] in the UK. LT (PICU) and NICU (JD) will lead this phase.

Research aim: The aim of the e-surveys is to establish what 'standard' practice is around GRV measurement in UK PICUs and NNUs.

Specific objective: To describe current unit (PICU and NICU) practices around the measurement of gastric residual volume

Method: A cross-sectional electronic survey across will be sent to all UK PICUs (n=27) and NNUs (n=190) using our established networks (sent on a link within an email). Our target response rate is >70% and to maximise our response rate we will send three reminders a week apart to these lead individuals. This method has been successful in previous work to generate optimal response rates.

Sample: We will ask the lead nurse, consultant and dietitian (or other designated nutrition focussed leads – if not the lead consultant and nurse) to collaboratively complete these surveys based on what their current practice is. We will also request they send any written guidance their unit has around enteral feeding to us. We require only one survey returned per unit and require a unit name/identifier only so we can identify non-responders and target them to maximise our response rate.

Instrument development: No previous survey instrument captures the data we need, thus we have developed a survey instrument for NICU and one for PICU. As per best practice in survey design, we will test these instruments for clarity and face validity on 10 individuals (nurses, doctors and

dietitian, who will not be involved in the true survey). The instrument will then be input into electronic software (RedCap) and checked for accuracy again with five separate individuals. We will try to reduce free text within the instrument, but will allow for comments. Each unit will be identifiable and we will ask the units to send any written feeding guidance they have to us. LT has undertaken some pilot work eliciting PICU nurses' views around GRV measurement in a single UK PICU [30] and this work has proven valuable, as there was confusion amongst nurses around the term GRV, which we will now clarify in this national survey.

Data collection We will conduct this through our national research networks, thus our sample size is 27 UK PICUs [Paediatric Intensive Care Audit Network, PICANet 2016] and 190 NNUs [National Neonatal Research Database NNRD] in the UK. LT (PICU) and NICU (JD) will lead this phase with assistance from the CTU.

Data analysis Data from this survey will be analysed descriptively, as is the intention of this survey. Inferential analysis is not required. Data will be exported from Redcap software in a CSV file format into Microsoft Excel where a summary of standard practice will be produced for a) NICU and b) PICU. This will form the basis for the proposed 'standard arm' of a future trial, to be agreed at the consensus meeting.

Work Package 2 – interviews and focus groups involving parents and healthcare professionals

Work package 2 is a qualitative study involving semi-structured interviews (telephone or face to face) with parents (of children who have experience of mechanical ventilation in a PICU or NICU) and focus groups with NICU and PICU practitioners (nurses, doctors and dietitians). KW will lead this phase.

Interviews will explore parents' views on:

- acceptability of the proposed trial;
- potential barriers to recruitment;
- participant information;
- whether they would be happy to consent for their child's participation in the trial; and
- potential patient-centred outcome measures.

Interviews and focus groups will explore healthcare professional's views on:

- acceptability of the trial including the proposed inclusion and exclusion criteria and clinical equipoise;
- acceptability of not measuring GRV and other measures used to assess feeding tolerance;
- willingness to randomise to a future trial; potential barriers to recruitment consent; and
- associated training needs.

Inclusion criteria:

- parents/carers of children with experience of ventilation in both NICU and in PICU in the last three years
- Practitioners (nurses, doctors and dietitians) working in NICU and PICUs

Exclusion criteria

- Unable to speak English.

Recruitment and sampling

Parents

Based on previous relevant studies[1 2] we aim recruit 20-30 parents (n= 10-15 in each setting) depending upon point of data saturation. This is when the major themes identified in new data are reoccurring from previous participants/ transcripts and no new major themes are being discovered.

We will recruit parents though three recruitment routes including: 1) social media or website adverts targeting charities and parent support groups (e.g. BLISS, Sepsis Trust, hospital charities); and 2) emails to our national contacts, including the PICANET Families group and if anticipated recruitment rates are low then 3) a advert in a local and/or national newspaper.

The RA will contact gatekeepers (e.g. charity leads/Chief Executive Officers) of support groups for parents whose children may have had experience of ventilation in both NICU and in PICU. The RA will ask them to post the GASTRIC advert on the support group's website and/or social media pages (e.g. Facebook and Twitter). If recruitment is poor, we may also place an advert in local and/or national newspapers. All adverts will include study information and contact details for parents to register their interest in taking part. A link to the study twitter site @GASTRICStudy and the GASTRIC website will enable parents to access further information including the full PIS.

Practitioners

We aim to hold 2-4 focus groups (e.g. 2 focus groups [one NICU, 1 PICU] in the north and 2 focus group [one NICU, 1 PICU] in the south). Each focus group will involve 8-12 practitioners. We will conduct up to 10 telephone interviews with practitioners who are unable to attend the focus group. We will recruit practitioners through email invitations, and adverts on the study website (e.g. GASTRIC website) and social media (e.g. Twitter, Facebook). The GASTRIC RA will send emails (including PIS) and target social media advertisements to groups including the Paediatric Intensive Care Society (PICS), the British Dietetic Association (BDA) Critical care group, the British Association of Perinatal Medicine (BAPM) and the UK Neonatal Networks for NNUs. Focus groups will be held in different geographical locations (e.g. North and South) which will be specified in recruitment materials. Clinicians will be asked to contact GASTRIC RA to register interest in taking part. Places will be allocated in order of registration of interest and by role to ensure we have a mix of practitioners represented (nurses, doctors and dietitians).

Arranging interviews and focus groups

Parent interviews

The GASTRIC RA will respond to parents' requests to participate by email or telephone (depending on which contact details are provided). The researcher will check eligibility. Where parents meet the eligibility criteria, the researcher will arrange a convenient time and date for the telephone or home (in North West England only) interview. A copy of the GASTRIC Study Parent Information Sheet (PIS) which includes a list of proposed GASTRIC outcomes will be sent to parents via email or post (whichever is preferred). Parents will be asked to read this PIS and outcomes list before the scheduled interview. Parents who do not meet the eligibility criteria, or register after the target sample size (10-15 in each setting depending upon data saturation point) has been reached, will be thanked for their time and will take no further part in the study.

Practitioner focus groups and interviews

The GASTRIC RA will confirm the time and location of focus groups with the practitioners. Telephone interviews will be arranged for up to ten practitioners who are unable to attend the focus group.

Informed consent

Telephone interviews

The RA 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 RA reading each aspect of the GASTRIC Participant Consent Form to participants, including consent for audio recording and to receive a copy of the findings when the study is

complete. The RA will tick each box on the consent form when the participant provides verbal consent and then sign the consent form. Informed consent discussions will be audio recorded for auditing purposes.

Home interviews

The RA will seek written informed consent for the study using the GASTRIC Participant Consent Form. The participant and the researcher will sign the consent form.

Focus groups

Written informed consent will be sought from practitioners prior to the commencement of focus groups

Interview and focus group conduct

The RA will check that the parent has had sufficient time to read the PIS (and list of outcomes for parent interviews). The interview will then commence using the interview or focus group topic guides which have been informed by previous trials conducted in paediatric emergency and critical care in the NHS[3 4], by earlier research (led by one of our co-investigators, KW)[2 5] and by a review of all potential outcome measures conducted for the study. Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress. At the end of the interview a £30 Amazon voucher will be given/posted to parents to thank them for their time. A GASTRIC Participant thank you letter will be posted to participants after interview and focus groups including a copy of the consent form.

Data analysis

Interviews and focus group data from work package 2 will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst analysis will be informed by the constant comparison approach of grounded theory, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (i.e. the design of the proposed trial and site staff training).

Work package 3 an e-Delphi study to get consensus on trial issues

This work package will investigate optimal trial design, primary and secondary outcome measures and inclusion and exclusion criteria. These will be sent to a broader range of stakeholders: PICU and NICU consultants, nurses and dietitians, BDA, PICS, BAPM, relevant researchers and trialists to ascertain their views on issues involving a trial of GRV versus no GRV measurement. Members of the study team are members of these networks and they will be approached via email to the chair, members and also through our meetings. This survey will build on information gained from WP 1 and 2 and the literature review. LT and the CTU both have experience in conducting Delphi studies. A modified two round e-Delphi study will be conducted across UK NNUs (Delphi 1) and UK PICUs Sample: In addition to PICU and NICU clinicians (nurses (all grades), doctors (registrars and consultants), dietitians), this survey will be sent to a broader range of stakeholders, which will include trialists and members of the professional societies (BDA, PICS, BAPM). We would aim for a minimum of 100 participants per survey (NICU and PICU). Instrument development is described below in data collection. We will recruit participants through our professional networks. Data collection: Participants will be required to participate in both rounds of data collection.

Round 1:

Based on our literature review of all studies of GRV measurement, we will summarise our findings succinctly as an introduction for survey participants around previously used trial designs, primary and secondary outcome measures and inclusion and exclusion criteria. Then we will ask them questions about their views on each of these points: 1) optimal trial design 2) optimal primary outcome measure 2) optimal secondary outcome measures 4) inclusion criteria and 5) exclusion criteria asking them to rank the above (on a Likert scale ranging from not important to extremely important. They will also be able to suggest any alternative options that they believe are important and have not already been proposed. For each question, the number of participants who have scored the question will be presented alongside the distribution of the score. All options that are provided in round 1 will be taken forward to round .As per best survey design practice, the survey instrument will be tested for clarity and face validity on 10 individuals (a mix of nurses, doctors and dietitians) not involved in the main study. The survey will be input into the electronic software (RedCap) and checked for accuracy again with five individuals.

Delphi Round 2:

At the start of round 2 each participant will be provided with the number or respondents to round 1 alongside the distribution of scores for each of the questions that has previously been asked.

Participants will be sent their score from round 1, asked to consider the results from other responders and then asked to re-score the question and make any final comments. Participants will also be asked to score any additional questions that have arisen from round 1. Any changes that are made to a participants score from Round 1 to Round 2 will be documented, participants who did not take part in round 1 will not be allowed to take part in round 2. For each question the number of participants who have scored the question and a distribution of the scores will be summarised. Each question will be classified as 'consensus in', 'consensus out' or no consensus according to the following classifications:

Definition of consensus

Consensus classification	Description	Definition
Consensus in	Consensus that the question should be included in the future study design	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3.
Consensus out	Consensus that the question should not be included in the future study design	70% or more participants scoring as 1 to 3 AND <15% participants scoring as 7 to 9.
No consensus	Uncertainty about question	Anything else

Work package 4 Analysis of national datasets for trial feasibility

Work package 4 will analyse the data gathered with regard to trial feasibility and use existing national databases (NNRD and PICANet) to determine the feasibility of collecting the data from these routine data sets, and explore potential eligible population of a future trial of GRV versus no GRV in UK PICUs and NNUs, including whether it is feasible to combine NICU and PICU into one trial. CG (NICU) and RP (PICU) will lead this phase in conjunction with the CTU. This phase will determine potential patient recruitment numbers, based on the agreed trial design and inclusion/exclusion criteria and calculate a sample size for the trial. Both these datasets are anonymous and two members of the study team (RP and CG) who will undertake this analysis are the managers of both these datasets.

The National Neonatal Research Database (NNRD) and Paediatric Intensive care Audit network (PICANet) are the two routinely collected datasets this feasibility study will use. The datasets do not collect exactly the same data, but have enough detail in them to achieve the aim of their use in this feasibility study. Their use will determine the potential eligibility of children in both specialities, based on agreed inclusion and exclusion criteria, stratification variables and outcomes, which would inform sample size and viability of a future trial from current UK data.

For example: If work streams 2 and 3 indicate that the neonatal component of the trial should include preterm infants <32 gestational weeks and target the outcomes necrotising enterocolitis (primary), death (secondary), weight SDS at discharge (secondary) and duration of parenteral nutrition in days (secondary); the following will be extracted from 2017 data held in the NNRD:

1. National UK population level event rates from 2017 for outcomes such as necrotising enterocolitis and death, and population level summary data for outcomes such as duration of parenteral nutrition and weight SDS at discharge. These data will be used to calculate sample size.
2. The number of annual eligible infants cared for in UK neonatal units, broken down by network. These data will allow estimation of geographical coverage and number of participating units.

NNRD

The NNRD holds data from all infants admitted to NHS neonatal units in England, Scotland and Wales (approximately 90,000 infants annually). The NNRD is formed from data extracted from the neonatal electronic health record system used by health professionals during routine clinical care. Briefly, daily clinical information on neonatal unit admissions is recorded in a point-of-care, clinician-entered Electronic Patient Record. A defined data extract, the Neonatal Data Set (NHS Information Standard SCCI595) is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster NHS Foundation Trust where patient episodes across different hospitals are linked, data are cleaned, and entered into the NNRD. Contributing neonatal units are known as the UK Neonatal Collaborative (UKNC). The NNRD is approved by the National Research Ethics Service (10/H0803/151), Confidentiality Advisory Group of the Health Research Authority (8-05(f)/2010) and the Caldicott Guardians and Lead Clinicians of contributing hospitals.

Data items

The NNRD holds the Neonatal Data Set, approximately 450 data items that form a NHS data standard:
http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_neonatal_data_set/national_neonatal_data_set_-_episodic_and_daily_care_fr.asp?shownav=0

Data items include demographic and admission items (e.g. maternal conditions, birthweight), daily items (entered every day for all infants, e.g. respiratory support, feeding information), discharge items (e.g. feeding and weight at discharge) and ad hoc items (entered if and when they occur e.g. suspected infection, ultrasound scan findings, abdominal x-ray findings).

Data quality

Data extracted from the neonatal Electronic Health Record are cleaned; records with implausible data configurations are queried and corrected by the treating clinicians. Cleaning is carried out by the Neonatal Data Analysis Unit before data are incorporated into the NNRD. The robustness of core NNRD data (birth weight, sex, length of stay and death) has been previously demonstrated for research purposes. Data held in the NNRD are used for multiple purposes including national audit (the HQIP funded National Neonatal Audit Programme) and analyses for the Department of Health, NHS England and the Chief Medical Officer.

PICANet

PICANet collects basic demographic and clinical data on all children admitted to designated Paediatric Intensive Care Units (PICUs) in the UK and Eire. Each admission constitutes an episode, and an individual may have a number of episodes within the database. Episodes may be aggregated by individual PICU or by census/administrative geographies using standard postcode lookup tables (the National Statistics Postcode Directory). PICANet has permission to collect patient identifiable data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001). PICANet collects data on demographics, admission characteristics, presenting physiology (to allow calculation of the expected probability of mortality for risk-adjustment), diagnostic information, clinical interventions and outcome. A full list of data items and data definitions can be found at www.picanet.org.uk/documentation.

Ensuring quality is part of the PICANet process. At input, internal logical, consistency and range checks are carried out within the software with an on-screen summary of outstanding validation checks on completion of a record for the data entry personnel on the unit. Units are able to access admission reports (amongst many others) that allow them to cross check against admission book and patient administration systems. This system of checks provide an ongoing audit of the data quality of the PICANet data. Validation visits are carried out annually to review a sample of records and crosscheck that the data submitted to PICANet corresponds with the data held within the patients clinical records. Detailed feedback is sent to the unit following these visits to ensure that any problems with data collection and abstraction can be dealt with locally

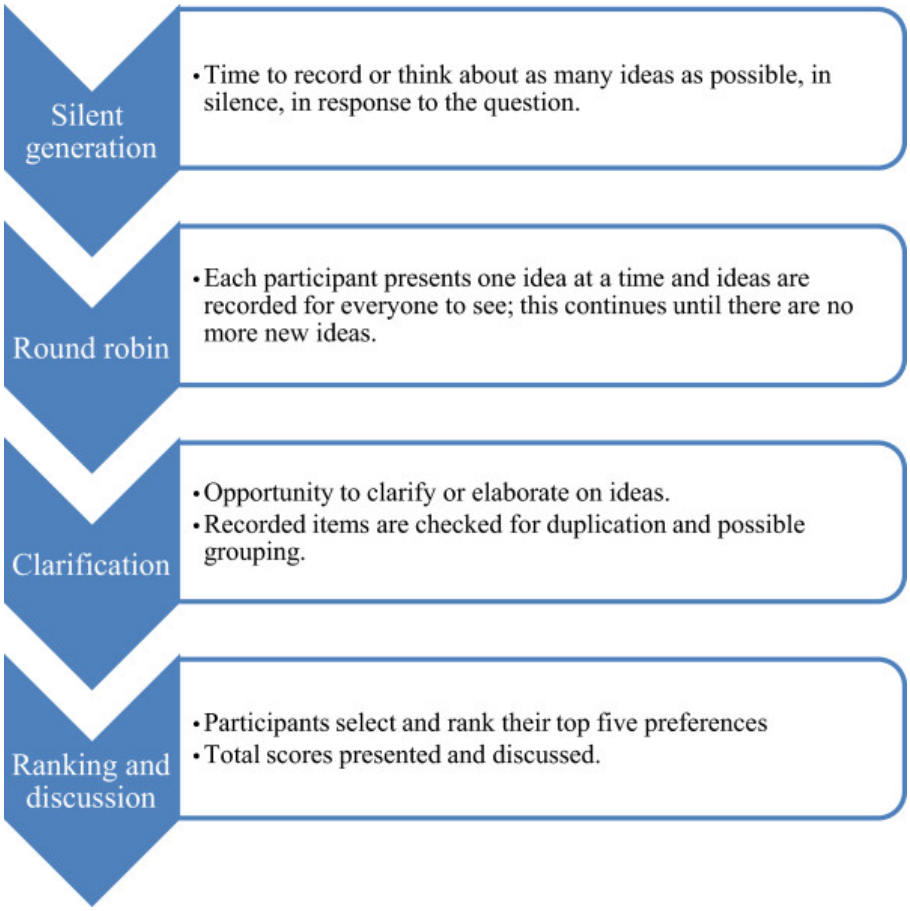
Work package 5 consensus meetings

Work package 5 will involve separate PICU and NICU face-to-face consensus meetings. The aim of these is to bring together key stakeholders in each speciality including national societies, parent groups as well as clinicians and researchers to review all the data gathered and get consensus on a routine GRV (control arm) and a no GRV (intervention arm) of a future trial. Two members of the

study team study (FV and AB) who work in a PICU and NICU (in France) where GRV is not routinely measured, will share their protocols, guidance, outcomes and experience. An adapted nominal group technique (aNGT) will be used to facilitate this consensus process formally. Any areas of disagreement and trial feasibility will be discussed and agreed with regard to a potential trial in each speciality. A skilled and independent facilitator will run this meeting with the involvement of the study team.

The process we intend to use for the consensus meetings is an adapted nominal group technique (aNGT). Tume has experience with this technique and NGT is a well-recognised process, both for research and clinical purposes to establish consensus amongst a group of stakeholders [40-43]. This technique is an efficient and very structured group meeting consensus process, which can achieve consensus easily within one meeting. NGT follows a number of steps outlined below. An independent skilled facilitator will lead these meetings, with Tume and Dorling. With consent from participants, the discussion from the meeting will be audio-recorded and transcribed to ensure no data is missed, once transcribed these audio files will be deleted. Participant quotes will not be used, they will be audio recorded purely to avoid missing any important data. Analysis of the data will be both quantitative and qualitative, using content analysis and analysis using rankings of items and mean item scores.

Figure A, below shows the steps in the adapted Nominal group technique described by McMillan et al[42].



Data analysis

Analysis of each work package will be undertaken separately. Analysis of the surveys will be undertaken descriptively only as per the aim of these surveys. The Delphi survey will be analysed descriptively and also using specialised Delphi software, held by the CTU. Analysis of the qualitative work (interviews and focus group data) will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst analysis will be informed by the constant comparison approach of grounded theory, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (i.e. the design of the proposed trial and site staff training). Analysis of the routine database data will be descriptive in nature but this will inform sample size calculations for a future trial. Analysis of the two consensus meetings using a aNGT process will be both quantitative and qualitative, using content analysis and analysis using rankings of items and mean item scores. The nine proposed outcomes in this feasibility study are clearly defined, thus the assessment of these will be undertaken as an ongoing process throughout the study with the study team, but will also be done formally at a final study team meeting at the end to integrate all the results.

Dissemination and projected outputs

Members of the study team are embedded within the UK PICU and NICU community and networks. We will provide ongoing updates during the feasibility study to the PICS-SG, the Neonatal study group meetings (the National Neonatal Network N3, the UK Neonatal Collaborative Network and the Neonatal Clinical Studies Group). Success of the study depends on the engagement of and collaboration with doctors, nurses and dietitians from across the UK PICUs and NNUs. A study Twitter account has been set up @GASTRICStudy to promote awareness of the study and a study webpage will provide more detailed information about the study both to a parent audience and to a professional audience.

Wider dissemination to the PICU and NICU community will be achieved through presentation at key national (PICS and RCPCH, European (ESPNIC, ESPR, jENS) and International meetings (PICC and COIN) and through publication in high impact journals in the specialities. PICS, ESPNIC, BAPM have multidisciplinary membership and associated academic journals. In accordance with open access policies proposed by the NIHR we will publish the findings of this feasibility study both in a focused PICU (Pediatric Intensive Care Medicine) and NICU (Archives of Diseases in Childhood, Fetal and Neonatal Edition) journal. This will make the results readily accessible to healthcare professionals. The results will also be disseminated through our networks within these communities described above. A final report will also be published in the NIHR HTA journal.

Dissemination to parents, the public, and the wider NHS: The results will also be actively promoted through social media (Twitter, Linkedin), the study twitter account and the study website to provide ongoing information about the study. With the input from our parent advisory group will also prepare a summary of the results for distribution with the parent and family groups (BLISS, ICU Baby Steps, PICANET Parents & Families Group and on social media).

There are nine intended outputs and deliverables from this feasibility study:

1) A clear indication of whether a trial of routine GRV versus no GRV is feasible in 1) UK PICUs and 2) UK NNUs in terms of: clinical equipoise, willingness to randomise and implement the intervention, patient recruitment and parent willingness to participate

2) A clear indication of whether this intervention (and a future trial) is acceptable to parents in both PICU and NICU

3) Clearly defined and agreed control (with routine GRV measurement) feeding guideline for 1) PICU and 2) NICU

4) Clearly defined and agreed intervention (no routine GRV measurement) feeding guideline for 1) PICU and 2) NICU (including a nurse education pack)

5) An agreed optimal trial design, including sample size estimation with clear inclusion and exclusion criteria, outcome measures and trial feasibility based on patient eligibility data

6) Parent information leaflet to explain the study and future trial

7) A clear indication of whether it is possible to combine PICU and NICU settings into one trial

8) An open access results paper for the PICU stream (Pediatric Critical Care Medicine)

9) An open access results paper from the NICU stream (Archives of Diseases in Childhood, Fetal and Neonatal Edition)

Through these outputs, we will ensure that the feasibility impacts upon the PICU and NICU community, patient and parent groups and a report to the HTA will determine whether progression to a full trial is feasible.

Plan of investigation and timetable:

A detailed plan and timetable for the study is outlined below over 18 months in the appendices.

Project management

This study involves a number of study team members spread geographically across the UK and France. To ensure effective team communication LT and the CTU will lead a monthly dial-in teleconference meeting to discuss project milestones, progress and issues arising. LT will coordinate the work for the overall project and lead the PICU work stream. Jon Dorling will lead the NICU work stream and KW will lead the qualitative work across both PICU and NICU. A shared folder in Dropbox (or similar) will contain all up-to-date study documents for access by team members. These mechanisms will ensure effective communication within the team.

Ethics

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki and those in Good Clinical Practice. As we will interview parents (as well as NHS staff) NHS approval review will be required from the HRA. This will be south through proportionate review by the lead applicant. All PICUs and NNUs in the UK routinely submit their data to PICANET (for PICU) and NNDA (for NICU). The routine data is already collected without consent and has been approved by the Patient Information Advisory group (now the NHS Health Research Authority Confidential Advisory Group).

Patient and Public Involvement

Our study will use an experienced PPI lead (JP) to coordinate a parental study group and ensure their ongoing involvement in all stages of this study. This parent study advisory group, which will comprise a minimum of two NICU and two PICU parents and will meet face to face or virtually twice a year or as needed. This group will provide detailed feedback into this feasibility study in terms of identifying relevant questions to ask parents and families, feedback on parental information needs, their views on the results and involvement in the Delphi and consensus phase of the study and dissemination of the results in a parent-friendly format back to users. JP will coordinate these parent group meetings, she will support the parents, provide training for parents as required and coordinate the outputs of this group.

Trial management and oversight committees

Study Management Group

All day-to-day management of the GASTRIC Feasibility Study will be the responsibility of the SMG. Members of the SMG will include the GASTRIC Study Coordinator, the Chief Investigator and the clinical co-investigators. The SMG will meet regularly to discuss management and progress of the GASTRIC Feasibility Study and findings from other related research.

Independent Study Oversight committee

The progress of the GASTRIC Feasibility Study will be monitored and supervised by the ISOC. At least 75% of the members will be independent (including the Chair). It will also consist of at least one service user representative, experienced paediatric and neonatal medicine and critical care clinicians, a statistician and the Chief Investigator/s.

Role of the Liverpool Clinical Trials Unit

Liverpool CTU will be responsible for the day-to-day management of the trial and will act as custodian of the study data, as delegated by the chief investigator. Secure data sharing amongst the study team will only involve anonymised data. KW and the University of Liverpool will act as the

custodian of the qualitative data, as delegated by the chief investigator and again will only be shared securely with the study team after anonymization.

Ethical compliance

The GASTRIC Feasibility study will be conducted in accordance with the approved Study Protocol, GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as Liverpool CTU's research policies and procedures.

Trial registration

This Trial has been registered with the ISRCTN Registry (**ISRCTN42110505)**

Central ethical compliance

The study will apply for HRA Ethical approval by the Chief investigator. Liverpool CTU will submit annual progress reports and all amendments to the GASTRIC protocol to the REC for review. Liverpool CTU will provide relevant approved study documents and other related materials to participating sites.

Participant confidentiality and data protection

No patient identifiable data will be collected as part of the study. If a parent/guardian consents for telephone interview, and/or longer term contact/future research then parent/guardian contact details will be required by the CTU and the University of Liverpool to complete successful follow-up. Liverpool CTU and University of Liverpool will act to preserve confidentiality and will not disclose or reproduce any information by which participant could be identified outside of that consented for. Data will be stored securely. LCTU is registered under the Data Protection Act (1998) and all CTU staff have undergone data Protection and ICH GCP training.

Sponsorship and indemnity

Sponsor details

Sponsor Name:	University Hospitals Bristol NHS Foundation Trust
Address:	Research and Innovation, Level 3, UH Bristol Education and Research Centre, Upper Maudlin Street, Bristol BS2 8AE. Tel: 0117 342 0233
Contact:	Diana Benton
Email:	R&DSponsorship@UHBristol.nhs.uk

Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG (96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Funding

The trial is supported by grant funding from the NIHR Health Technology Assessment (HTA) Programme, as part of the Fever Feasibility Study grant (16/94/02) A written agreement with the site PI and/or the PI's institution and UHB will outline the funding arrangements to sites. The SMG will meet and review the financial aspects of the trial at least report to the Sponsor.

Publication policy

The final report, including a detailed description of the GASTRIC Feasibility Study results and recommendations for future policy and practice and future research, will be submitted to the HTA

Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All participant data will be anonymised before publication. A publication plan with author order and intended journals, detailing five papers has been agreed by the SMG.

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