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# Determining Optimal Outcome Measures in a Trial Investigating No Routine Gastric Residual Volume Measurement in Critically Ill Children

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## Abstract

**Background:** Choosing trial outcome measures is important. When outcomes are not clinically relevant or important to parents/patients, trial evidence is less likely to be implemented into practice. This study aimed to determine optimal outcome measures for a trial of no routine gastric residual volume (GRV) measurement in critically ill children. **Methods:** A mixed-methods approach was used: a focused literature review, parent and clinician interviews, a modified 2-round Delphi, and a stakeholder consensus meeting. **Results:** The review generated 13 outcomes. Fourteen pediatric intensive care unit (PICU) parents proposed 3 additional outcomes; these 16 were then rated by 28 clinicians in Delphi round 1. Six further outcomes were proposed, and 22 outcomes were rated in the second round. No items were voted “consensus out.” The 18 “no-consensus” items were voted in a face-to-face meeting by 30 participants. The final 12 outcome measures were time to reach energy targets, ventilator-associated pneumonia, vomiting, time enteral feeds withheld per 24 hours, necrotizing enterocolitis, length of invasive ventilation, PICU length of stay, mortality, change in weight and markers of feed intolerance (parenteral nutrition administered), feed formula altered, and change to postpyloric feeds all secondary to feed intolerance. **Conclusion:** We have identified 12 outcomes for a trial of no GRV measurement through a multistage process, seeking views of parents and clinicians. (*JPEN J Parenter Enteral Nutr.* 2020;00:1–8)

## Keywords

child; enteral feeding; intensive care; nutrition; pediatric; trials

## Clinical Relevancy Statement

Twelve relevant outcomes have been identified for a trial of no routine gastric residual volume measurement in critically ill children.

## Introduction

Selecting the most appropriate outcome measures for a trial is increasingly recognized as important for trial evidence to be effectively implemented into clinical practice.<sup>1</sup> Ensuring trial outcomes are both clinically relevant and important to parents and patients is vital to optimize the impact of the research and to improve implementation and uptake into practice.<sup>2</sup> In addition, heterogeneity of clinical trial outcomes is a problem across clinical medicine but is more pronounced in relatively “small” specialties such as pediatric

critical care, in which many trials are single centered<sup>3</sup> and underpowered. In such “small” specialties, synthesis of trial results is essential for evidence-based practice, but unfortunately, the pooling of trial results in meta-analyses is often not possible because of outcome heterogeneity. This work, as part of a larger funded feasibility study, sought to determine the optimal parent and clinician outcome measures for a future trial of no routine gastric residual volume (GRV) measurement to guide enteral feeding in pediatric critical care. The proposed future trial of no routine GRV measurement (compared with standard care involving regular GRV measurement) to guide enteral feeding in critically ill children was called the GASTRIC trial.<sup>4</sup> This was a National Institute for Health Research (NIHR)–funded mixed-methods feasibility study to determine whether it was possible to conduct a future trial in UK pediatric intensive care units (PICUs).

## Methods

A mixed-methods study was undertaken between March 2018 and April 2019 as part of a larger NIHR Health Technology Assessment (HTA)-funded study (GASTRIC Reference16/94/02). The trial was registered on the ISRCTN registry (42110505). There were 4 phases involved in identifying the optimal outcomes:

1. A focused literature review to identify outcomes used in previous clinical trials and observational studies of GRV in any critically ill populations: including adults and preterm neonates. Databases were searched (Medline, CINAHL, ProQuest) in March 2018 by L.N.T. using the search terms: "gastric residual" and "gastric aspirate" in critically ill patients. For included studies, detailed data on each outcome measure used were extracted into a data collection form for summarizing.
2. Parent interviews: Qualitative researchers (L.R. and E.D.) recruited parents with experience of tube feeding in PICUs in the last 3 years through 4 routes. These included the use of social media, national contacts, word of mouth, and newspaper advertisements. Parents were excluded if they did not speak English. Once eligibility was confirmed, an interview date and time were scheduled. A participant

information sheet, with a list of potential outcomes developed from the focused literature review, was emailed to parents to read prior to the interview. Based on previous research, it was anticipated that 10–15 parents would be recruited to reach data saturation point.<sup>5</sup> This is when the major themes identified in new data are recurring from previous interviews and no new major themes are being discovered in analysis.<sup>6</sup> Interviews explored views on the proposed GASTRIC trial. The last section of the interview included a series of questions to determine what outcomes parents felt would be important to measure in the proposed trial and then asked parents to rank them by importance. Full details of the outcome prioritization process are reported in a previous study conducted by members of our team.<sup>7</sup> Content analysis<sup>8</sup> was then used to identify outcomes to inform the subsequent Delphi study.

3. Delphi study: A modified 2-round Delphi method was used,<sup>9</sup> and an e-survey was developed (Supplementary File S1), derived from information gained from the literature review and the parent interviews. The survey was pilot-tested for clarity and face validity with 10 individuals (a mix of nurses, doctors, and dietitians) and then tested again within the study team. It was then input into Delphi-Manager Software.<sup>10</sup> Key healthcare professional

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Conflicts of interest: L. N. Tume is an NIHR HTA panel member. J. Dorling reports grants from NIHR, during the conduct of the study for the study, grants from NIHR; and grants from Nutrinia, outside the submitted work. The grant from Nutrinia in 2018 was for part of his salary to work as an expert advisor on a trial. J. Dorling was a member of the NIHR HTA General Board (from 2017 to 2018) and the NIHR HTA Maternity, Newborn and Child Health Panel (from 2013 to 2018). C. Gale reports grants from Medical Research Council and the NIHR during the conduct of the study and grants from NIHR, Mason Medical Research Foundation, Rosetrees Foundation and from Canadian Institute for Health Research outside the submitted work. He reports grants and personal fees from Chiesi Pharmaceuticals outside of the submitted work; the grant is for a research study and the personal fee was to support attendance at an educational meeting. C. Gale is vice-chair of the NIHR Research for Patient Benefit London Regional Assessment Panel and has sat on the panel since 2016. F. V. Valla reports personal fees from BAXTER and personal fees from NUTRICIA outside the submitted work.

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stakeholder groups were identified as UK-based, research-engaged PICU nurses, PICU doctors, pediatric surgeons, and PICU dietitians. Participants were invited to take part via email, through their professional networks (British Dietetic Association [BDA], Pediatric Intensive Care Society [PICS], and its associated study group PICS-SG). The target number of respondents was 40, and automated reminders were sent weekly via the survey software. Participants were allocated a unique identifier to allow identification of individuals completing all rounds of the Delphi exercise.

Round 1 of the survey consisted of a succinct summary of the review findings by way of an introduction (previously used trial designs and primary and secondary outcomes), a question to establish respondents' stakeholder group, and a set of outcomes to score (Supplementary File S1). Participants were invited to score the importance of each of the outcomes listed using a 9-point Likert scale as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group,<sup>11</sup> with 1–3 labeled "not important," 4–6 labeled "important but not critical," and 7–9 labeled "critical." Participants were able to provide comment on outcomes and were asked to suggest any additional outcomes that they thought were relevant (Supplementary File S1). Outcomes were listed alphabetically to avoid potential weighting of outcomes caused by the order in which they were displayed. For each outcome, the number of participants who scored the outcome and the distribution of scores (percentages of who had scored each outcome) were summarized by stakeholder group. At the end of round 1, the study management group reviewed the suggested additional outcomes and identified new distinct outcomes to add to the next round. In round 2, participants were presented with a summary of the results of round 1 (histograms of scores for each outcome and each stakeholder group) and asked to rescore these outcomes. They were also asked to score any additional outcomes suggested in round 1. Finally, they were asked to specify a single primary outcome.

Outcome scores for each round were summarized using descriptive statistics and histograms, split by stakeholder group. Free text responses were listed. The round 2 scores were used to formulate consensus statistics for each outcome by stakeholder group and, overall, the percentage of respondents that scored 7, 8, or 9 (outcome rated critical); the percentage that score it 1, 2, or 3 (outcome rated unimportant); and consensus status ("consensus in," "consensus out," "no consensus") (Table 1).

**Table 1.** Definition of Consensus Status.

Consensus status	Description	Definition
Consensus in	Consensus that the outcome should be included in a future study design	70% or more participants scoring as 7–9 AND <15% of participants scoring as 1–3 in each group
Consensus out	Consensus that the outcome should not be included in the future study design	70% or more participants scoring as 1–3 AND <15% of participants scoring as 7–9 in each group
No consensus	Uncertainty about the outcome	Anything else

- Face-to-face consensus meeting: The aims of this meeting were to review the results of the mixed-methods study, vote on outcomes that did not reach consensus in the Delphi survey, and discuss future trial feasibility and design. Parents were invited to this meeting along with PICU healthcare professionals from all the UK PICUs. A skilled and independent facilitator led this meeting with the involvement of the study team. Voting results were summarized using the same methodology as described for the Delphi. Ethical approval was obtained from the University of the West of England in April 2018 (REF HAS.18.04.144).

## Results

### Literature Review

A focused review of the literature to identify previous trials and studies around GRV measurement in all critically ill populations was undertaken in March 2018. Six studies were identified that studied GRV, 1 in the pediatric population,<sup>12</sup> 3 in critically ill adults,<sup>13–15</sup> and 2 in critically ill preterm neonates.<sup>16,17</sup> All the outcomes reported in these studies have been summarized into 14 outcomes (Table 2). Two of these outcomes (days receiving parenteral nutrition and days of central venous line access) were relevant only for preterm infants and thus removed, and others (gastrointestinal morbidity) were separated into vomiting and diarrhea as separate outcomes, generating 13 items from the literature review.

Figure 1 shows the flowchart detailing the generation of outcomes across all stages of the study.

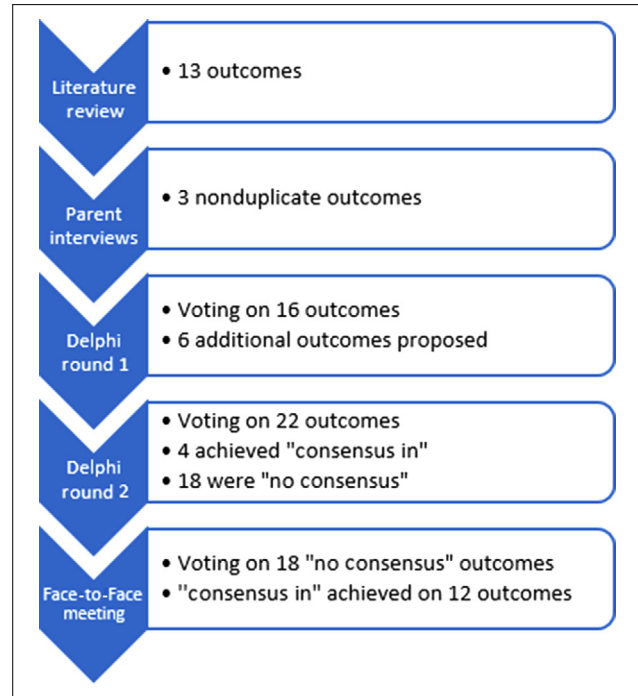
**Table 2.** Outcomes Identified in Previous Studies of GRV Measurement.

Outcome	Patient population
1. Intensive care unit length of stay	All
2. Hospital length of stay	All
3. Length of invasive ventilation	All
4. Occurrence of ventilator-associated pneumonia	Adult and pediatric
5. Achievement of predicted energy goals using various definitions: Proportion of patients achieving 100% Cumulative energy deficit over 7 days Ratio of prescribed/achieved energy target Enteral feeding "adequacy" Median daily volume of feed given Percentage of predicted energy requirement achieved per day Time to achieve full feeds for preterm neonates (120 mL/kg and 150 mL/kg/d)	Adult, pediatric, and neonatal
6. Occurrence of necrotizing enterocolitis	Neonatal and pediatric
7. Incidence of GI intolerance: vomiting, diarrhea, abdominal distention, feed intolerance, gastroesophageal reflux	Adult and pediatric
8. Nursing time spent measuring GRV	Adult
9. Growth (weight) from admission to discharge	Neonatal and pediatric
10. Growth (length) from admission to discharge	Neonatal
11. Days of PN	Neonatal
12. Days of central venous catheter (to deliver PN)	Neonatal
13. Time spent receiving nothing by mouth (no enteral feed) in 24-hour period	Adult
14. Survival	All

GI, gastrointestinal; GRV, gastric residual volume; PN, parenteral nutrition.

### Parent-Important Outcomes

Fourteen PICU parents were interviewed regarding 10 children (4 sets of parents were interviewed separately about their child), and 6 out of 10 children had had a previous neonatal unit admission. Interviews took place an average of 11 months (range, 8–37 months) after PICU admission. The children's cause of PICU admission varied: congenital heart disease (n = 4), sepsis (n = 2), airway (n = 1), and complications of congenital conditions (n = 3). The parents proposed 7 outcomes of importance; 4 of these were duplicate items generated from the literature review. The 3 nonduplicate parent-reported outcomes were long-term feeding issues, being "back to their normal self," and longer-term outcomes (after hospital discharge).

**Figure 1.** Study flowchart indicating how final outcomes were obtained.

### Delphi Study

A total of 16 outcomes were included in round 1 of the Delphi. In November 2018, 45 PICU healthcare professionals were invited to take part in the Delphi survey. Of these, 30/45 (67%) registered for the survey, 28/45 (61%) went on to score the 16 outcomes in round 1, and of these, 22/28 (79%) went on to complete round 2. Six distinct outcomes were suggested by respondents in round 1, making 22 outcomes to be scored in round 2. Sixty-four percent (14/22) of respondents changed their score for at least 3 outcomes from round 1 to round 2. "Consensus in" was achieved on only 4 outcomes by all 3 professional groups: incidence of gastrointestinal morbidity (vomiting); incidence of ventilator-acquired pneumonia (VAP); duration of time with no enteral feed per 24-hour period; and the time to achievement of estimated energy requirements. All outcomes scored in round 2 are shown in Table 3, together with the source of the outcome and consensus status. No outcomes were voted "consensus out." Respondents were asked their choice of primary outcome measure for a future trial, and 8/22 (36%) preferred time to achievement of energy targets, with 5/22 (23%) choosing incidence of VAP.

### Consensus Meeting

Twenty-six PICU healthcare professionals (4 dietitians, 9 physicians, 12 nurses, and 1 general surgeon) attended the consensus meeting on April 2, 2019; some of these had

**Table 3.** Percentage of Participants That Scored 7, 8, or 9 for Each Outcome Scored in Round 2 of the Delphi Study, by Stakeholder Group.

Outcome	Source of outcome	PICU doctors and pediatric general surgeon (n = 11)	PICU nurses (n = 8)	PICU dietitians (n = 3)	All (n = 22)	Consensus status
Time to achievement of predicted energy goals	LR	90.9% <sup>a</sup>	<sup>a</sup> 87.5% <sup>a</sup>	<sup>a</sup> 100% <sup>a</sup>	90.9% <sup>a</sup>	In
Incidence of ventilator-acquired pneumonia	LR	<sup>a</sup> 81.8% <sup>a</sup>	<sup>a</sup> 87.5% <sup>a</sup>	<sup>a</sup> 100% <sup>a</sup>	86.4% <sup>a</sup>	In
Time feed stopped per 24 hours	LR	<sup>a</sup> 81.8% <sup>a</sup>	<sup>a</sup> 87.5% <sup>a</sup>	<sup>a</sup> 100% <sup>a</sup>	86.4% <sup>a</sup>	In
Incidence of necrotizing enterocolitis	DR1	<sup>a</sup> 90.9% <sup>a</sup>	<sup>a</sup> 87.5% <sup>a</sup>	66.7%	<sup>a</sup> 86.4% <sup>a</sup>	None
Incidence of GI morbidity: Vomiting	LR	<sup>a</sup> 72.7% <sup>a</sup>	<sup>a</sup> 87.5% <sup>a</sup>	<sup>a</sup> 100% <sup>a</sup>	81.8% <sup>a</sup>	In
Length of time IV	LR	63.6%	<sup>a</sup> 75% <sup>a</sup>	<sup>a</sup> 100% <sup>a</sup>	<sup>a</sup> 72.7% <sup>a</sup>	None
Mortality	LR	63.6%	62.5%	<sup>a</sup> 100% <sup>a</sup>	68.2%	None
Length of stay: PICU	LR	63.6%	62.5%	66.7%	63.6%	None
Total length of time respiratory support (IV + NIV)	LR	63.6%	50%	<sup>a</sup> 100% <sup>a</sup>	63.6%	None
Nursing time spent measuring GRV	LR	54.5%	50%	<sup>a</sup> 100% <sup>a</sup>	59.1%	None
Length of stay: Hospital	LR	63.6%	37.5%	66.7%	54.5%	None
Administration of parenteral nutrition secondary to feed intolerance	DR1	45.5%	37.5%	66.7%	45.5%	None
PP feeding (placing a PP tube) secondary to feed intolerance	DR1	27.3%	50%	<sup>a</sup> 100% <sup>a</sup>	45.5%	None
Change in weight (growth) between PICU admission and discharge	LR	27.3%	50%	66.7%	40.9%	None
Long-term feeding issues	Parents	27.3%	37.5%	33.3%	31.8%	None
GI morbidity: Diarrhea	LR	9.1%	37.5%	66.7%	27.3%	None
Long-term outcomes (after hospital discharge)	Parents	36.4%	25%	0%	27.3%	None
Administration of prokinetic drugs secondary to feed intolerance	DR1	18.2%	12.5%	66.7%	22.7%	None
Looking and/or behaving like their normal self	Parents	18.2%	25%	0%	18.2%	None
Change in length (growth) between PICU admission and discharge	LR	18.2%	12.5%	33.3%	18.2%	None
Change to feed formula type secondary to feed intolerance	DR1	0%	25%	66.7%	18.2%	None
Parental satisfaction	DR1	9.1%	0%	33.3%	9.1%	None

DR1, Delphi round 1; GI, gastrointestinal; GRV, gastric residual volume; IV, invasive ventilation; LR, literature review; NIV, noninvasive ventilation; PICU, pediatric intensive care unit; PP, postpyloric.

<sup>a</sup>“Consensus in” criteria were met:  $\geq 70\%$  scored 7, 8, or 9 and  $< 15\%$  scored 1, 2, or 3.

<sup>b</sup>“Consensus in” criteria met in all groups.

participated in the Delphi study. Despite 2 parents agreeing to participate, no parents were able to attend on the day. The professionals represented 13 different UK PICUs out of a possible 27. At this meeting, there was discussion and subsequent voting on the 18 outcomes that did not reach consensus in the Delphi study. Using the same scoring criteria as the Delphi survey, 8 items were voted "consensus in," 6 were voted "consensus out," and 4 failed to reach any consensus (Table 4). The choice of the 2 primary outcome

measures, time to achieve estimated energy requirements and VAP, was presented and their feasibility discussed, but no voting took place on these. The final list of the 12 consensus outcomes for a future trial is presented in Table 5.

## Discussion

This is one of the few studies in pediatric critical care to use a robust process to identify outcomes of importance for both

**Table 4.** No-Consensus Items Voted on at Consensus Meeting.

Outcome	Consensus Status
Administration of parenteral nutrition secondary to feed intolerance	In
Change to feed formula type secondary to feed intolerance	In
Change in weight (growth) between PICU admission and discharge	In
Incidence of necrotizing enterocolitis	In
Length of time IV	In
Length of stay: PICU	In
Mortality	In
PP feeding (placing a PP tube) secondary to feed intolerance	In
Administration of prokinetic drugs secondary to feed intolerance	None
GI morbidity: Diarrhea	None
Length of stay: Hospital	None
Total length of time respiratory support (IV + NIV)	None
Long-term feeding issues	Out
Long-term outcomes (after hospital discharge)	Out
Looking and/or behaving like their normal self	Out
Nursing time spent measuring GRV	Out
Change in length (growth) between PICU admission and discharge	Out
Parental satisfaction	Out

GI, gastrointestinal; GRV, gastric residual volume; IV, invasive ventilation; NIV, noninvasive ventilation; PICU, pediatric intensive care unit; PP, postpyloric.

**Table 5.** Final 12 Outcomes Gaining Consensus for a Trial of NO GRV Measurement.

Time to achievement of predicted energy goals (full feeds)
Incidence of ventilator-acquired pneumonia
Duration of time with no enteral feed per 24 hours
Incidence of GI morbidity: Vomiting
Incidence of necrotizing enterocolitis
Length of time invasive ventilation
Length of stay: PICU
Mortality
Change in weight (growth) between PICU admission and discharge
Administration of parenteral nutrition secondary to feed intolerance
Change to feed formula type secondary to feed intolerance
PP feeding (placing a PP tube) secondary to feed intolerance

GI, gastrointestinal; GRV, gastric residual volume; PICU, pediatric intensive care unit; PP, postpyloric.

parents and clinicians for a future trial.<sup>5,18</sup> It is also the first to examine this in the context of a trial of no routine GRV measurement to guide enteral feeding in pediatric critical care. More recently, others have used this process in trials of fluids and temperature control in pediatric critical care.<sup>5,18</sup> The importance of choosing the most appropriate outcome measures for a clinical trial is increasingly recognized.<sup>1</sup> When trial outcomes are either not clinically relevant or not considered important to parents/patients, the evidence generated is less likely to be adopted and implemented into clinical practice. This is costly and inefficient and leads to

research waste.<sup>19</sup> Increasing efforts are being made to robustly identify and use the most appropriate trial outcomes for all stakeholders, including patients and parents. To try to overcome these issues, the development of standardized core outcome sets (COSs) for patient populations is encouraged.<sup>20</sup> The Core Outcome Measures in Effectiveness Trials (COMET) initiative aims to do this by developing and agreeing on a set of outcomes known as a COS.<sup>20</sup> These are an agreed minimum set of outcomes that should be reported in all trials of a specific disease or population.<sup>2</sup>

Of interest were the differences between clinical-suggested and parent-suggested outcomes, especially with respect to the longer-term issues after intensive care discharge. Previous studies exploring prioritized outcomes by parents<sup>5,18</sup> have shown that parents who are interviewed shortly after a child's PICU admittance prioritized shorter-term outcomes, which were potentially most relevant to them at the time of being interviewed. However, parents in this study were interviewed on average 11 months after PICU discharge, and ongoing issues of importance to them were more highly ranked as outcomes.

The final list of 12 agreed outcomes for a future trial comprises nutrition outcomes (achievement of energy goals, time spent without feeds, gastrointestinal morbidity, and outcomes secondary to feed intolerance), adverse events (VAP and necrotizing enterocolitis [NEC]), and measures of morbidity (length of invasive ventilation and PICU length of stay). Nutrition outcomes are clearly important in a trial of any nutrition intervention, yet all previous adult trials were powered on adverse events (VAP). Conversely, previous neonatal trials, although measuring NEC (a condition far



more common in preterm neonates), targeted nutrition outcomes (time to achieve full enteral feeds) as the primary outcome. Healthcare professionals are highly concerned about adverse events<sup>21</sup> and fear these potentially more than they value improved outcomes in any new interventional trial. However, the incidence of both VAP and NEC is very low in pediatric critically ill children;<sup>22-24</sup> therefore, powering any trial based on these outcomes would require such high numbers of eligible children to make a trial very difficult. When we asked clinicians to choose their preferred primary outcome measure, the nutrition outcomes of time and the achievement of target energy goals were most commonly selected. In pediatric critical care, the choice of outcome for trials of nutrition interventions is important, as mortality is too low to be feasibly used to power trials (unlike adult critical care). In addition, nutrition outcomes and their impact may be more important for children than for adults, given that children need to grow (as well as not lose weight) during critical illness. This becomes more important as the length of time spent critically ill increases.

Currently, no COS exists for pediatric critical care or for trials of nutrition interventions; however, adult work has begun to generate a COS for adult critical care nutrition trials. Future research to gain international consensus on core outcomes and incorporate these standardized outcomes in clinical nutrition and pediatric critical care trials is essential and is planned in collaboration with professional societies.

Our study has several strengths. The approach taken used a formalized approach and identified potential trial outcomes from previous research and from parents with experience of PICU care. In addition, the professionals who attended the consensus meeting were not all the same as those participating in the Delphi study, thus generating a broader perspective, although there was some overlap. However, there are also some limitations that warrant mentioning. Some of the PICU parents also had experience of neonatal care, which may have influenced their prioritization of longer-term outcomes and of the outcomes themselves. The sample size for the Delphi was limited to UK PICU professionals, specifically those with an interest in research, and was small, which may limit the generalizability of these results to the wider group of PICU health professionals. We targeted this group because this work was to determine the feasibility of a UK trial within a publicly funded healthcare system, and we therefore wanted to involve and engage with UK PICU clinicians about a future trial; there was, however, representation from the 3 main professional groups involved in enteral feeding. We did not include parents in the Delphi survey, primarily because we felt asking the parents at the interview was the most appropriate way to gain meaningful input; however, the lack of parent attendance at the consensus meeting was a limitation and may have led to the final consensus results being less representative of parent views. We utilized

all means to get parents to attend (and payment for their time and travel was provided), but caring commitments on the day prevented parents who had expressed interest from attending the consensus meeting. Future work should consider providing childcare to enable parents to attend. Not having parents at this meeting is a limitation that may have impacted on some parent-focused outcomes being voted out. For the future trial, we will work further with our expert parent group to ensure that outcomes of importance to the parents are captured.

## Conclusions

Given the increasing importance placed on determining the optimal outcome measures for trials, this paper describes a robust process to identify optimal outcomes for a future trial of no routine GRV measurement to guide enteral feeding in pediatric critical care. Using the most appropriate trial outcomes increases the likelihood that future trial results are both meaningful to parents/patients and implemented in clinical practice.

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## Statement of Authorship

L. N. Tume and J. Dorling equally contributed to the conception and design of the research; H. Hickey, K. Woolfall, E. Deja, L. Roper, A. Beissel, and F. V. Valla contributed to the design of the research; H. Eccleson, K. Woolfall, E. Deja, L. Roper, J. Preston, I. Andrzejewska, N. Pathan, and L. Latten contributed to the acquisition and analysis of the data; B. Arch planned and carried out all quantitative statistical analyses, A. P. Jones, L. N. Tume, C. Gale, and J. Dorling contributed to the interpretation of the data; and L. N. Tume drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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