

PhD Research Proposal: Evaluating the evidence for using a volume-based enteral nutrition algorithm within a pediatric intensive care unit

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Part A: Background and significance

Background: The most critically ill patients in children's hospitals are in the pediatric intensive care unit (PICU). Some of these children have acute (e.g. trauma, burns, or post-surgery) and/or chronic illnesses (e.g. malignancies, cystic fibrosis, and chronic kidney, congenital heart, gastrointestinal and neuromuscular diseases)¹ which predispose them to malnutrition as well as adverse outcomes^{2,3}. Malnutrition is a problem in Canadian children's hospitals with prevalence of 1 in 5 children⁴. Malnourished children are at higher risk of hospital-acquired infections and mortality than their well-nourished counterparts¹. Further complicating pre-existing malnutrition is the fact that nutritional status often worsens during hospital admission, at least in part due to interference with patients' nutrition support for frequent interventions and assessments^{2,5}. Addressing malnutrition is an identified priority for the American Society for Parenteral and Enteral Nutrition (ASPEN)⁶.

Solutions to mitigate the effects of malnutrition in critically ill children include providing enteral nutrition (EN)^{2,7,8}. Early, optimal, enteral energy and protein intake have been associated with better clinical outcomes including mortality^{2,7,8}. Unfortunately, frequent feed interruptions in PICUs are common with interruptions occurring on two or more PICU days for the majority of patients² resulting in underfeeding and cumulative nutrient deficits^{2,9}. Traditionally in pediatrics, EN is ordered and provided using hourly rate-based goals, which direct the bedside nurse to run the feeding pump at a prescribed hourly rate. The problem with this approach is that the nurse is not authorized to compensate for feed interruptions. Using a daily volume-based EN algorithm would circumvent this issue by allowing bedside nurses to adjust feeds to be able to deliver the 24-hour prescribed goal and compensate for feed disruptions.

Current literature comparing volume-based with rate-based EN in hospitalized critically ill adults is of low certainty. One small, randomized control trial (RCT)¹⁰, one pilot RCT¹¹, and several small quasi-experimental trials¹²⁻¹⁶ have suggested that volume-based EN may improve nutrition delivery and clinical outcomes including feed tolerance¹⁴, hospital length of stay¹⁵, and decreased muscle loss¹¹. The applicability of adult research to pediatrics is questionable given the differences between children and adults nutritional needs as well as heterogeneity within and between these patient populations. ASPEN/Society of Critical Care Medicine guidelines on feeding the critically ill child have identified the need for randomized trials to address questions about improving nutrition delivery in the PICU⁶. These guidelines identify key clinical outcomes of importance which include PICU and hospital length of stay, hospital-acquired complications, and duration of mechanical ventilation⁶.

Significance: The proposed randomized feasibility trial will provide evidence for recruitment, enrollment, algorithm adherence, the deferred consent model, and baseline data to inform sample size calculations for a future RCT evaluating the use of volume-based EN to improve nutritional adequacy and clinical outcomes for critically ill children. The findings may inform the design of a larger RCT powered to detect changes in clinically relevant outcomes, which could inform knowledge translation in PICU clinical practice guidelines including the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines, Alberta Health Services' Nutrition Practice Guidelines, and the Canadian Critical Care Society. Understanding and exploring the barriers and facilitators to change and implementation of a new feeding algorithm may improve translation of study findings to stakeholders including bedside nurses.

Part B: Preliminary studies

Observational studies in critically ill children found achieving nutritional adequacy via EN can be safely delivered and may improve clinical outcomes such as mortality, length of stay, and infections^{2,7}. Providing early and adequate EN during PICU admission may be associated with fewer adverse effects of malnutrition^{2,7,8}. A large, multi-center, retrospective cohort of over 5000 children, found that EN initiation within the first 48 hours of admission was associated with reduced odds of mortality¹⁷ and reduced hospital charges¹⁸ after adjusting for severity of illness, age, and site. In another large prospective cohort of critically ill children, underweight children had higher odds of 60-day mortality³. In this cohort, higher enteral energy intake was associated with lower 60-day mortality (67% compared to 33% of goal energy) after adjusting for severity of illness and site². Concerning, average enteral energy intakes were low at 38% of goal and enteral feed interruptions occurred on at least 2 days for most (71%) patients². Enteral protein intake >60% of goal was also associated with lower odds of mortality, and interruptions to enteral feeds were associated with lower enteral protein delivery⁷. However, the timing of when to initiate EN remains a topic of debate, especially in sicker children such as those with sepsis on inotropic support and children on extracorporeal membrane oxygenation.

Consensus guidelines on feeding critically ill children recommend initiation of early EN, within the first 48 hours of PICU admission⁶. Cohort studies demonstrated that early EN was well tolerated and was associated with improved markers of nutritional status, decreased caloric deficits, weight loss, and protein breakdown in critically ill children¹⁹⁻²². The several RCTs on this topic have been small and of limited generalizability due to specific patient populations (burns)^{23,24} and study quality²⁵. Although guidelines for feeding critically ill children recommended the use of early EN⁶, no systematic review has been conducted to synthesize and evaluate the quality of evidence for early EN in PICU. Therefore, a systematic review on this topic is warranted to facilitate evidence-informed feeding practices in PICU.

Interruptions to enteral feeds is a well-known barrier to adequate EN in PICUs. A recently published international study of PICU nurses, physicians, and dietitians ranked feeds being withheld in advance of procedures and operating room visits as the top barrier to EN⁵. Keehn et al⁹, in a prospective cohort of critically ill children, found that EN was interrupted an average of 1.2 times per child per admission resulting in 12 hours of missed feeds. Additionally, these children spent 42% of their PICU admission without any form of nutrition support. Work is underway in both PICUs and ICUs to reduce total fasting time prior to surgery²⁶.

To our knowledge, all studies on the ICU practice of volume-based enteral feeding protocols have been conducted among adults. Studies suggest improved nutrition delivery and adequacy. However, only three of nine studies observed important changes in clinical outcomes^{11,14,15}. None of them were powered to assess changes in mortality and length of stay.

A pilot RCT of 60 mechanically ventilated adults found an association between volume-based EN and improved energy and protein intake compared to rate-based EN¹¹. Additionally, they assessed muscle mass using ultrasound to measure quadricep muscle layer thickness. After adjusting for baseline quadricep muscle layer thickness, and controlling for age, severity of illness, body mass index, and admission diagnosis, volume-based EN was associated with less muscle loss at discharge.

One RCT which compared volume-based to rate-based EN algorithms was carried out among critically ill ventilated adults¹⁰. The group fed via the volume-based algorithm had higher nutrition

received, lower energy deficits, and on days when feeds were interrupted, received a higher percentage of goal calories. Concerning, this small study (n=63 subjects) changed their allocation ratio (from 1:1 to 3:1) partway through due to poor study enrollment. Blinding was not mentioned, raising concern about potential bias in the study's conduct and analysis. Also, they reported poor compliance by bedside nurses to the volume-based EN algorithm. They did not stratify the subjects or adjust for the potential modifying effect of illness severity. The clinically relevant outcome of length of stay was not included. Due to the considerable limitations of this study, and their use of an adult population, it does not inform us of whether or not volume-based EN is a superior practice in a PICU.

We found seven quasi-experimental before-and-after studies that compared volume-based to rate-based EN algorithms in adult intensive care unit (ICU) patients^{12-16,27,28}. All seven of these studies found a higher percentage of goal energy received in the volume-based group (their primary outcome). These studies varied in their approaches in terms of secondary outcomes considered (ventilation duration^{12,14,15,28}, length of stay^{12,15,27,28}, and mortality^{12-15,27}). Adjusting for illness severity changed one study's findings to non-significant¹², while this did not alter the significance of a second study's results¹⁴. Due to the before-and-after study designs, there was no randomization or blinding in these studies to lower the risks of bias.

A recently published systematic review and meta-analysis on the topic found that critically ill adults fed using volume-based EN achieved significantly more of their goal energy intake and had significantly reduced ICU length of stay and length of mechanical ventilation compared to adults fed using rate-based EN²⁹. The study authors included seven studies (four RCTs and three cohort studies), with six of the studies classified as high quality. These findings need to be interpreted with caution as the review was incomplete leading to questionable conclusions. The authors only screened 40 title abstracts. They excluded before-and-after studies in their design which make up a large base of literature on this topic. This resulted in missing at least three relevant studies (14-16). Additionally, the three studies they included as cohort studies were in fact before-and-after studies^{12,27,28}, which could impact how they scored study quality using the Newcastle Ottawa Scale (NOS)³¹. They did not provide a breakdown of the NOS score. Of the three observational studies reviewed, only one controlled for confounding variables¹² such as severity of illness in their analysis. Studies that did not control for confounding should have been considered low study quality and the impact of study quality on outcomes should have been explored in their meta-analysis.

It is not known if changing children and adolescents' feeding in PICUs from rate-based EN to volume-based EN improves nutrition delivery or if clinical outcomes are improved. There are limited RCTs on this topic, all have been small, and completed in adult ICUs. Care of pediatrics differs from adults in ways that may impact the feasibility of implementation of a volume-based algorithm. The heterogeneity of ages and how children are fed at different ages (infants, child, adolescent) require more specialized feeding interventions. We believe that a volume-based EN algorithm can accommodate for the different formulas, feeding rates, and feeding volumes that will be required in pediatric care. Therefore, clinical equipoise justifies a trial as described in this proposal.

Part C: Specific aims

Significance/Aim: The goal of my PhD research program will be to 1) systematically evaluate the current literature pertaining timing of EN within pediatric critical care; 2) complete a randomized feasibility trial to assess participant enrollment and recruitment, adherence of healthcare staff to the

study protocol, and evaluate the proposed deferred consent strategy; and 3) qualitatively assess nurses' perceptions and experiences of the implementation of the volume-based EN algorithm.

Part D: Experimental design and methods

SYSTEMATIC REVIEW – UNDERWAY

Co-author: Emma Schalm

1: Systematic review

Rationale: Although guidelines for feeding critically ill children recommended the use of early EN⁶, as far as we are aware no systematic review has been conducted to synthesize and evaluate the quality of evidence for early EN in PICU. Therefore, a systematic review on this topic is warranted to facilitate evidence-informed feeding practices in PICU.

Focused research question: Is early enteral nutrition in critically ill children admitted to a pediatric intensive care unit associated with better clinical outcomes as compared to delayed enteral nutrition?

Overview and Definitions: This study will be conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines³² is registered on PROSPERO (CRD42021286271).

PICOD: The *population* of interest is critically ill children admitted to PICU. The *intervention/exposure* is early EN independent of the number of calories or amount of protein intake. Early EN is defined as enteral nutrition/feeding initiated ≤ 48 hours of patient admission to PICU or as defined by the study investigators. The comparator is delayed EN defined as enteral nutrition/feeding initiated > 48 hours of PICU admission or as defined by the study investigators. The *primary outcome* is mortality in PICU and/or hospital. *Secondary outcomes* include other clinical indicators such as length of stay (LOS) in PICU and/or hospital, 28-day ventilator free days, gastro-intestinal/feed intolerance, ventilator associated pneumonia, changes in anthropometric measurements, adverse events and additional outcomes included in studies. Due to the limited nature of the literature around early EN in pediatric critically ill populations, the study *designs* included in this review will be RCTs, quasi-experimental, observational cohort (prospective or retrospective), and case-control studies.

Search Strategy

The online databases Medline, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINHAL), and Cochrane Central Register of Controlled Trials (CENTRAL) will be searched. In addition, two reviewers will search the bibliographies of all identified relevant full manuscript publications and all abstracts of both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) scientific conferences within the last five years. Clinical trial registries will be consulted to identify any potentially relevant ongoing trials (clinicaltrials.gov, isrctn.com, vacsp.gov).

Experts in the field, including Krista Wollny, and Dr. Lori Bechard, will be contacted for information about potential ongoing or unpublished studies. With the assistance of a Medical

Librarian the search strategy will be developed and revised in Medline and will be used as the basis for the search strategies in the other databases listed.

Controlled vocabulary terms (e.g., MeSH terms) and keywords will be searched for the following three themes:

1. Enteral nutrition
2. Intensive care and pediatric intensive care
3. Pediatric population using a population specific search filter for each database ³³⁻³⁶.

Themes will be combined using the Boolean operator “and” in different combinations.

Due to the inconsistent language used to define early EN, broad scope of relevant clinical outcomes, and limited number of studies anticipated, we will not limit search terms for our intervention/exposure to “early” EN, use study design filters, or specify our search outcomes to keep our search broad and prevent omitting relevant articles. No restrictions will be placed on language, date, or country of publication.

Identification of Articles Eligible for Full-Text Review:

Upon execution of the search strategy and identification of articles for title & abstract screening, two reviewers will independently determine which articles are eligible for full-text review in Covidence ³⁷. An abstract will be considered eligible if it:

1. Reports on original data from an original study
2. Compares early EN with delayed EN
3. Was conducted at least partially within a PICU

Studies conducted solely in neonatal or adult ICU will be excluded. Studies on non-human subjects will be excluded. If it is unclear whether a study meets the inclusion criteria at title & abstract screening, it will be included for full-text screening. Articles will proceed to full-text review if at least one investigator believes it satisfies the inclusion criteria to support sensitivity at this stage. Agreement between reviewers will be quantified using inter-rater reliability (IRR) Kappa coefficient ³⁸. Note, reviewers will pilot test citation screening before commencing title & abstract screening.

Identification of Articles Eligible for Inclusion in Systematic Review (and Possible Meta-Analysis):

The two reviewers will proceed to full-text review of the eligible articles independently and in duplicate. The following inclusion criteria will be used in the full-text review:

1. The population is critically ill children ≤ 18 years of age admitted to PICU
2. The intervention/exposure is early EN (defined as enteral feeding initiated ≤ 48 hours from PICU admission or as author specified)
3. The comparator is delayed enteral nutrition (defined as enteral nutrition initiated > 48 hours from PICU admission or as author specified)

4. The outcome is a marker of clinical outcomes (including but not limited to mortality, LOS, 28-ventilator free days)
5. The study employed quantitative methods to explore the relationship between enteral feeding initiation and clinical outcomes
6. The study design is RCT, quasi-experimental, observational cohort (retrospective or prospective), or case-control

Studies that employ solely qualitative methods will be excluded. Case studies or case series will be excluded. Studies conducted in neonatal ICU, adult ICU or general hospital units outside of intensive care will be excluded. Studies will be excluded if we cannot access the peer-reviewed manuscript or data (if in the process of publication). For an abstract to be included we will contact authors and require the peer-reviewed manuscript or data. For an article to be deemed eligible for inclusion in the systematic review, both reviewers must agree. Disagreements will be resolved by discussion and consensus or involvement of a third reviewer. The Kappa coefficient of inter-rater agreement will be calculated with an accompanying interval estimate.

Data Extraction Elements

Study data will be extracted independently and in duplicate from all articles included after full-text review using standardized data extraction forms in Excel developed and piloted by study authors. A data extraction form was developed to collate the information from each identified study (see Figures 3 for a text version of the Excel extraction form).

Non-randomized study quality was assessed using the Newcastle-Ottawa Scale (NOS), which scores cohort studies across three quality indicative categories: i) selection, ii) comparability, and iii) outcome assessment/exposure ascertainment³¹. The Cochrane Risk of Bias (RoB) tool will be used to assess study quality for randomized studies across five domains: i) randomization process, ii) deviations from intended interventions, iii) missing outcome data, iv) measurement of outcome, and v) selection of reported results³⁹.

Synthesis Approach

We will present data on the number and characteristics of the studies identified for systematic review and, if appropriate, the number and characteristics of trials identified for meta-analysis. We will use the PRISMA flow diagram to present the number of the studies identified, excluded with reasons for exclusion, and included in the final systematic review³². Of articles included, flow charts will indicate the numbers of articles that are RCTs and those that are not.

Depending on heterogeneity considerations, a pooled analysis of identified trials will be undertaken in STATA⁴⁰. Statistical heterogeneity will be assessed using the I^2 statistic. We expect heterogeneity within included studies and thus will use a random effect meta-analytic model. Meta-regression will be conducted to explore sources of heterogeneity and associations between potential co-variables (i.e., study design, country of publication, participant demographics) and clinical outcomes. Sensitivity analyses will be performed to evaluate the impact of poor-quality study design or publication date on the pooled estimate of clinical outcomes. Publication bias will be evaluated by calculation of Begg's rank test and Egger's regression test, and by visual inspection of a funnel plot^{41,42}. Meta-analysis results will be represented in a table and forest plot. The relative risk between children who received

early EN compared to children who received delayed EN will be assessed for our primary outcome measure mortality in PICU and/or hospital and secondary outcomes length of stay in PICU and/or hospital, 28-day ventilator free days, gastro-intestinal/feed intolerance, ventilator associated pneumonia, changes in anthropometric measurements, and adverse events.

Studies defined as high quality will be analyzed as a subgroup. We anticipate significant heterogeneity and will likely utilize stratified analysis by patient/study characteristics including age, sex, severity of illness, ventilation mode, feeding route, and admission diagnosis.

If study outcomes are too heterogeneous to conduct a quantitative synthesis, a qualitative synthesis will be conducted.

RANDOMIZED FEASIBILITY TRIAL

2: Randomized feasibility trial

The aim of this trial is to determine if a RCT evaluating a volume-based EN algorithm in pediatric critical care will be feasible.

Research question:

Feasibility trial: Can a RCT evaluating a volume-based EN algorithm compared to a standard of care rate-based EN algorithm be successfully run in a PICU?

Future RCT: In critically ill children being enterally fed in a PICU, will a volume based EN algorithm improve energy adequacy and protein adequacy, feed tolerance, infections, changes in anthropometric measurements at transitions of care, 28-day ventilator free days, length of stay, 60-day mortality, and 60-day hospital readmission compared to a rate based EN algorithm?

Objectives:

The primary objective is to assess the feasibility of the proposed RCT to evaluate a volume-based EN algorithm in the ACH PICU by:

- 1: Assessing participant enrollment and recruitment,
- 2: Assessing adherence of medical and nursing staff to the study protocol, and
- 3: Evaluating the proposed deferred consent strategy.

The secondary objective will be to obtain data to inform sample size calculations for nutrition (energy and protein adequacy) and clinical outcomes (feed tolerance, infections, changes in anthropometric measurements at transitions of care, 28-day ventilator free days, length of stay, 60-day mortality, and 60-day hospital readmission) for a larger RCT.

Significance

This proposed randomized feasibility trial will provide evidence on the feasibility of conducting a larger RCT evaluating the use of volume-based EN to improve nutritional adequacy during PICU admission and improve hospital outcomes for critically ill children. The findings of a larger RCT may inform knowledge translation through PICU clinical practice guidelines including Alberta's Nutrition Practice Guidelines, the Canadian Critical Care Society, the American Society of Parenteral

and Enteral Nutrition (ASPEN) guidelines and European Society of Pediatric and Neonatal Intensive Care (ESPNIC) nutrition guidelines.

Trial design: We will conduct a single-center parallel partially blinded 1:1 randomized feasibility trial of 20 children admitted to the Alberta Children's Hospital (ACH) PICU. The randomized trial will compare a volume-based EN algorithm (intervention) versus the standard of care rate-based EN algorithm (control).

Participants: Children admitted to the ACH PICU requiring enteral nutrition support.

Inclusion criteria: Children 1-month post-natal age to 18 years of age, anticipated by the intensivist or nurse practitioner to be admitted to the PICU for ≥ 48 hours and to be started on EN support will be eligible to participate.

Exclusion criteria: Children who have contraindications to EN (i.e., a non-functional GI tract), who are on exclusive parenteral nutrition, who are being fed by a bolus feed regime, who cannot progress past trophic feed volumes within 24 hours of EN initiation, who are undergoing palliation/withdraw of care, or who are anticipated to be admitted to PICU for <48 hours.

Planned interventions: In the first 24 hours of EN, feed initiation and advancement to goal hourly rate will be consistent for the two groups to allow time for randomization to occur. After randomization, bedside nurses will follow the feeding algorithm according to the child's random allocation.

Volume-based EN algorithm: Bedside nurses will receive a total daily feed volume prescription to be administered to the child over a 24-hour period. The bedside nurse will calculate the initial hourly rate by dividing the total daily feed goal by 24 hours at approximately 0700 hours. In this intervention group, they will be instructed to titrate the rate of feeds to accommodate for any feeding interruptions as follows: When feeds are held for > 1 hour, the remaining daily feed volume will be divided by the remaining number of hours. A maximum infusion rate will be set at 2 times the patient's baseline 24-hour feed rate to ensure that a large bolus volume of feed is not administered over a too short period of time. For example, standard practice is to hold EN 4 to 6 hours prior to extubation or operating room visits and to restart feeds within 4 hours of task completion (feedings are expected to be turned off for a maximum of 8-10 hours). Therefore, it is reasonable to assume that we will be able to make up most missed enteral feed volume with a maximum infusion rate of 2 times the 24-hour feed rate.

Rate-based EN algorithm (standard of care): Bedside nurses will receive an hourly feed rate to be administered over a 24-hour period. If feeds are held, they will be restarted at the same consistent hourly rate that was previously ordered. Nurses will not adjust feed rates to compensate for feed interruptions.

Mitigation of risk: There is a risk that children being fed via the volume-based EN algorithm could receive a larger volume of enteral formula over a short period of time when making up missed feeds after a child is off EN for an extended portion of the day. This larger volume could increase risk of feed intolerance and emesis that theoretically could increase the risk of stomach content aspiration. We will mitigate this risk by specifying maximum infusion rates capped at 2 times the patient's baseline 24-hour feed rate to a maximum of 6 mL/kg per hour up to 150 mL/hour⁴³.

We are not concerned about the larger volume exceeding the children's ability to manage for two reasons. First, children in the PICU are given less nutrition than their ambulatory, growing counterparts due to their lower energy expenditure. Their estimated goal enteral feed volumes are based on basal metabolic rate equations, which are approximately 2/3 the goal volumes delivered to children outside the PICU. Second, using continuous EN, children receive hourly feed rates that are less than 1/3 of what they would receive relative to bolus feeding given every 3 hours or meal eating approximately 3 times per day. We feel that capping our maximum infusion rates as specified above at twice the patient's baseline 24-hour feed rate will ensure feeds will run at rates that are physiologically safe. We will monitor daily changes in feed tolerance including incidence of emesis, diarrhea and abdominal distension in all children being fed using our volume-based EN algorithm. Adult studies comparing volume to rate-based EN algorithms have not reported an increase in feed intolerance including emesis in the volume-based EN group^{10,13-15}. One of these studies reported less emesis in the volume-based EN group¹⁴.

Ethics: We will seek ethics approval from Conjoint Health Research Ethics Board before this study proceeds. We will be requesting a deferred consent model^{44,45}. There is growing evidence that requesting consent close to admission to a PICU puts undo stress on caregivers and results in reduced study enrollment^{46,47}. Deferred consent facilitates randomization of eligible children at the decision to initiate EN and start the study intervention while providing time to approach caregivers. As our study question has equipoise between study arms and our interventions are not likely to pose undo harms to children, we feel a deferred consent model is appropriate. Informed consent by parents/guardians along with assent from older children and adolescents will be obtained by a PICU research nurse separate from the PICU medical team. Decisions to refuse consent or withdraw consent at any time will be respected and if this occurs, the patients will be assigned the standard of care rate-based feeding.

Randomization: Participants will be randomly allocated using stratified randomization in a 1:1 ratio to the intervention arm (volume-based EN algorithm) or the control arm (standard rate-based EN algorithm). Randomization will be block-stratified by age and ventilator support to ensure similar distributions between groups. Age will be stratified into three groups: infants (1 month to ≤ 1 year), children (> 1 year to ≤ 10 years), and pre-/adolescents (> 10 years to ≤ 18 years). We chose these age strata because of differences in the feeding products provided: infants (1 month to ≤ 1 year) will receive infant formula or breast milk, generally children (> 1 year to ≤ 10 years) will receive pediatric enteral formula, and adolescents (> 10 years to ≤ 18 years) will receive adult enteral formula. Children will be stratified into two ventilation categories, invasive ventilation (intubation) or no invasive ventilation (all other non-invasive/no ventilatory support). We chose to stratify by ventilatory support (intubated versus non-intubated) as intubation may influence how enteral feeds are prescribed and delivered. Randomization will be computer generated, concealed, and block-stratified using the allocation generator (www.randomizer.at) when each recruited patient is enrolled in the study. We will randomly vary block size (four to six subjects) to reduce the likelihood of investigators predicting allocation arm during randomization.

On weekdays the Study Coordinator will identify eligible children starting EN during daily rounds and will inform the Research Coordinator. The Research Coordinator will perform computer generated randomization, notify the Study Coordinator of allocation, and the Study Coordinator will give a sealed, opaque envelope with study allocation to the bedside nurse. The Study Coordinator will ensure that for each weekend day there will be one person on call for randomization.

On weekends the charge nurse will identify eligible children during bedside rounds and will call the on-call member of the research team for randomization. After web-based randomization the research team member will inform the charge nurse of allocation. The charge nurse will give a sealed, opaque envelope with allocation to the bedside nurse.

Blinding: A double-blinded strategy is not feasible for this study because the medical team cannot remain adequately blinded to study arms after randomization. Bedside nurses delivering EN support need to know which feeding algorithm to follow. The medical team (including PICU physicians, nurse practitioners, and dietitians) have access to patients' medical records which include current hourly infusion rates of enteral feeds so they can deduce the patients' allocations. The team uses current hourly infusion rates to assess fluid balance and to make clinical decisions.

To minimize bias, the research assistant tasked with data collection will remain blinded to study allocation throughout data collection and will enter the data into the REDCap database in a blinded fashion. This will be accomplished by instructing the research assistant to only access daily total volumes (not hourly volumes) from the electronic medical record. Additionally, after data collection and prior to data analysis, all identifying information (name, birthdate, age, diagnoses) will be saved in a separate file by the research assistant to ensure that the Study Coordinator, Nicole Gilbert (PICU dietitian and Master's Student), will be re-blinded to participant allocation during data analysis. The patients' age will be needed for the growth assessments. Before removing the patients' age from the analysis file, the research assistant will translate the patients' anthropometric measurements (weight, height, weight-for-length, body mass index) into z-scores based on the World Health Organization (WHO) growth charts using the Canadian Pediatric Endocrine Group's calculator (<https://apps.cpeg-gcep.net/>).

Primary outcomes:

Assess participant enrollment and recruitment: We will evaluate the proposed inclusion/exclusion criteria, participant recruitment, and enrollment. On weekdays, during bedside rounds, the Study Coordinator will compare eligibility of admitted children against our inclusion/exclusion criteria and document total number who are eligible. On Mondays, the Study Coordinator will compare patients who were admitted over the weekend with the inclusion/exclusion criteria. After randomization, the number of children who successfully initiate the study protocol will be documented.

Assessing adherence of the health care team to the study protocol: The Research Assistant will evaluate adherence to the allocated feeding algorithm over the last 24h period via the electronic medical record. The Research Assistant will document if a deviation from the allocated feeding algorithm (volume-based or rate-based) occurred in the study database. If a participant is removed from the study protocol it will be recorded by the Research Assistant along with the reason for removal provided by the most responsible medical practitioner.

Evaluating the proposed deferred consent strategy: As far as we are aware, there have been no studies using a deferred consent model in an enteral nutrition RCT. Therefore, part of this feasibility study will assess the deferred consent strategy. Quantitative evaluation of the deferred consent strategy will include the proportion of eligible subjects who provide consent/assent as well as the length of time it takes between randomization of eligible participants to starting the assigned feeding algorithm to obtaining consent/assent. The Research Assistant tasked with obtaining consent will also record the amount of time that elapses from randomization of a participant to the study protocol to receiving deferred consent.

Qualitative methods will be used to assess guardians/caregiver and patient perception and experiences around deferred consent. Participants will be selected through purposive sampling of parents/guardians of patients enrolled in both arms of the EN trial. Zoom semi-structured interviews will be conducted. Interviews will be recorded for data analysis. A minimum sample size for interviews set a-priori will be 10, with additional interviews theme saturation in reached⁴⁸. Data collection will be stopped once no new themes emerge.

Secondary outcomes:

Energy and Protein: Energy adequacy will be assessed by comparing patients' actual energy intakes to the prescribed energy goals for each patient, which are based on either the World Health Organization predictive equations to estimate basal metabolic rate⁴⁹ and/or measured using indirect calorimetry when clinically indicated and available. Daily prescribed calories and daily received calories will be collected while children are receiving EN. Protein adequacy will be assessed by comparing patients' actual protein intakes to the prescribed protein goals based on the Critical Care Society of Medicine/American Society for Parenteral and EN guidelines⁶.

EN route (gastric versus post-pyloric) will be collected for all days receiving EN. All sources of calories and protein including EN, intravenous fluids, and any parenteral nutrition received will be collected. Enteral formula energy and protein density will be standardized by age into infants (1 month to ≤ 1 year will receive 0.68 kcal/mL), children/ adolescents (>1 year to ≤ 18 years will receive 1.0 kcal/mL) and be consistent across study arms. Enteral formula energy and protein density will only be increased based on clinical need (i.e., fluid restriction, increased protein requirements) as per standard practice.

Anthropometric measurements: Nutritional status at admission to PICU, discharge from PICU, and discharge from hospital will be assessed using changes in anthropometric measurements including weight, length/height, weight for length/body mass index (BMI), and mid upper arm circumference (MUAC). Any of the following will be classified as malnourished: Weight for length (< 2 years old), BMI (≥ 2 years old), MUAC z scores of ≤ -2 and/or height for age z scores ≤ -3 ⁵⁰. The Research Assistant will ensure that anthropometric measurements are re-measured before discharge from the PICU, and again at discharge from hospital.

Feed tolerance: Feed intolerance will be collected from the medical record. Feed intolerance in a 24-hour period will be defined as new onset >2 episodes of diarrhea, >2 episodes of emesis, and/or abdominal distention that results in holding feeds. If feeds are held due to feed intolerance, they will be restarted at the previously tolerated hourly rate or at the discretion of the health care team.

Days on invasive ventilation (intubation), non-invasive ventilation (continuous positive airway pressure or bilevel positive airway pressure), nasal prongs (high flow O₂ and low flow O₂) or no support, days on inotrope medications, episodes of culture positive infections while in PICU, length of stay, and mortality in PICU will be collected at PICU discharge. Ventilator free days, defined as days alive and free from invasive ventilation, will be collected from PICU admission to 28 days after admission⁵¹. Total hospital length of stay, 60-day mortality, and 60-day readmission will be collected. Potential confounding variables collected in the PICU will include age, sex/gender, Pediatric Risk of Mortality Score (PRISM IV)⁵² (severity of illness), admission diagnoses, and admission comorbidities.

Sample size: We have done a preliminary sample size calculation for a fully powered RCT based on a published before-and-after intervention study in adult critical care. This study found a 13.4%

increase in mean percent energy received in their volume-based EN group¹⁴. In discussion with an expert in pediatric critical care research (LB) from Boston Children's Hospital we decided upon a meaningful effect size for this study of a 10% increase in mean percent energy received in the intervention arm. We used the mean percent prescribed calories received of 86.9%¹⁴ and an assumed common standard deviation of 13.8¹⁴ for the power calculation. A sample size of 31 children per study arm is needed to achieve 80% power with a 5% significance level using a two-sample t-test. To account for attrition and missing data we will recruit an extra 20%, that is 40 subjects per intervention arm. For our feasibility study, we will recruit 25% of this estimated sample which will be 10 subjects per intervention arm. Caution must be taken when using feasibility data to make estimations for larger studies and we will assess results of this feasibility study along with published adult literature when estimating a sample size for a full randomized trial on this topic⁵³.

Proposed duration of treatment: The duration of use of the volume-based EN algorithm will be from study enrollment to discontinuation of EN or transfer out of PICU, whichever comes first.

Frequency of follow up: The duration of daily study follow up will be from PICU admission to hospital discharge. Anthropometric measurements will be taken at admission, transfer out of the PICU to general inpatient units and at discharge from hospital. Children will have mortality information and length of stay in hospital collected upon discharge from hospital, 60-day mortality and readmission will be collected at 60-days or more post discharge from the electronic medical record.

Recruitment rate and timeline: In 2019, 121 children (approximately 10 per month) who met inclusion criteria for our proposed study were admitted to the ACH PICU. Over the past year, we have had fewer children admitted that met inclusion criteria due to the altered PICU admissions by COVID-19 (children rarely required ICU admissions when they had COVID-19 and there were reduced PICU admissions for seasonal flus and colds during 2020-2021). We expect that PICU admissions will gradually return to normal. We anticipate obtaining 85-95% of consents from children and their guardians⁵⁴. If we estimate that half of the eligible children admitted in 2019 (approximately 10 per month) would be eligible and agree to participate in our study, we will have an enrollment rate of 5 children per month. Our study recruitment will take place over approximately 6 months to 1 year.

Concerns with compliance: Adherence of bedside nurses to the volume-based algorithm may be a concern. We will reduce non-compliance by involving PICU stakeholders including nurse educators and bedside nurses, and knowledge users (including provincial representatives from nutrition services and international collaborators) in the development of the study protocol and volume-based EN algorithm. The adult RCT this topic had low nursing compliance to the volume-based protocol at 32%¹⁰. The authors did not provide any description regarding how nurses were trained and supported throughout the study. Despite poor compliance there was still a significantly lower mean energy deficit in the intervention arm.

We will conduct multiple training sessions to ensure bedside nurses have received adequate training on the new volume-based feeding algorithm prior to study initiation. The site Research Coordinator (NG Trainee and unit Dietitian) will provide support to nurses while patients are enrolled within the study. We will develop an electronic feed rate calculator saved on each nurse's computer to facilitate fast and easy calculations of enteral feed rates when children are fed via the volume-based algorithm.

Anticipated rate of loss to follow up: There is low likelihood that children who are randomized to our study will be lost to complete follow-up, as follow-up will occur throughout PICU admission and transitions of care within a single institution. We will minimize missing anthropometric measurements by tasking the Research Assistant with taking anthropometric measurements on-site Monday through Friday. They will assess for anticipated weekend discharges on Friday and take measurements if discharge over the weekend is likely.

Attrition due to study withdrawal is one possible source of missing data/loss-to follow up. We anticipate this number will be small. In McClave et al.'s RCT of Volume versus rate-based EN algorithms 6 of 63 (10%) subjects withdrew from the study due to early extubation prior to feed initiation or because family requested withdrawal of life-sustaining treatments¹⁰. Our study design includes children who are both intubated and receiving other ventilatory support, therefore extubation will not directly change eligibility to participate in the study.

Analysis plan:

Primary objective:

Assess participant enrollment and recruitment: The total number of children admitted to the PICU and the total number of children who meet inclusion criteria will be reported. After randomization, the total number of children who successfully initiate the study protocol will be reported. The proportion of eligible children who were successfully randomized as per protocol will be reported.

Assessing adherence of health care staff to the study protocol: The average number of deviations from the allocated feeding algorithm per participant and the average proportion of days on enteral nutrition when a participant is fed not according to protocol will be reported. Additionally, the total number of participants who were removed from the study protocol will be reported along with the reason why participants were removed.

Evaluating the proposed deferred consent strategy: Quantitative evaluation: The proportion of participants who provided consent/assent will be reported. The mean number of hours from randomization to obtaining consent will be reported. Qualitative methods using the Theoretical Domains Framework⁴⁸ will be used to assess parents' perceptions and experiences related to the deferred consent strategy.

Secondary objective:

We will prepare descriptive statistics such as tables and figures, to examine the secondary outcomes between the two groups. Analysis will occur at the end of study data collection. Analysis of the continuous variables mean percent daily prescribed protein received, anthropometric z scores change at transition to units and out of hospital, and PICU and hospital length of stay will be reported as means and standard deviations or medians and interquartile range if skewed. Categorical variables feed tolerance, 28-day ventilator free days, 60-day mortality, and 60-day hospital readmission. Length of stay will be reported as medians and interquartile range. Block-stratified randomization should lower the chances of confounding by age and ventilatory support. Effect modification and confounding by sex, admission diagnosis, admission comorbidities, nutritional status at admission to PICU, PRISM IV scores, route of EN, inotropic support, and mortality will be considered for the full-scale trial through regression analysis.

In the full-scale trial, Intention-to-treat analysis in its standard form will be used and this conservative approach will minimize type 1 error⁵⁵. Alpha value will be pre-set at 0.05, and exact p-values and 95% confidence intervals will be reported for all statistical analyses. All analyses will be performed using STATA© 16.1⁵⁶. This feasibility study will provide estimates of means, medians, and variability that can be used, along with results from the systematic review of adult literature, to estimate the sample size needed to conduct a full-scale RCT.

Trial management: Ms. Nicole Gilbert, Clinical Dietitian and Trainee, will oversee the coordination of this study within the ACH PICU. Consent will be obtained by the PICU Research Coordinator who is not involved in the day-to-day care of children within the PICU. Web-based Randomization software (randomizer.at) will be used to conceal and block-stratify randomization. Data collection will be conducted by a Research Assistant using the electronic medical record and entered into a secure REDCap database while keeping patient identifiers in a separate file, using random study id numbers. Data analysis will be conducted by the Trainee Nicole Gilbert.

Funding: This feasibility trial is being funded by the ASPEN Rhodes Research Grant.

Timeline: Approval for the proposed randomized feasibility trial has been received from ACH PICU Research Committee. We are awaiting ethics approval within the next month.

MIXED METHODS

Rationale: Successful implementation of enteral feeding practice changes in PICUs requires collaboration by front line nurses who are responsible for feed delivery. Nurse driven enteral feeding algorithms may improve successful implementation of enteral feeding in ICUs⁵⁷. However, as far as we are aware nurses' perceptions and experiences to changes in feeding practices within PICUs is not well described. An adult RCT on volume versus rate-based enteral feeding had reported low nursing compliance to the volume-based protocol at 32%¹⁰. The authors did not provide any description regarding how nurses were trained and supported throughout the study. Despite poor compliance there was a significantly lower mean energy deficit in the intervention arm. It is unknown if improved compliance would have changed the outcomes of this study. The authors of this study did not explore barriers to successful implementation of their study protocol. Understanding and exploring the barriers and facilitators to change and implementation of a new feeding algorithm may improve dissemination and translation of study findings to stakeholders including bedside nurses.

Objectives: 1: To evaluate adherence to a new volume-based EN algorithm compared to that of a rate-based EN algorithm at the Alberta Children's Hospital PICU (quan). 2: To assess nurses' perception and experiences of the implementation of the volume-based EN algorithm to explore facilitators and barriers to successful implementation that may arise which can inform design of larger trials (QUAL).

Theoretical framework: The Theoretical Domains Framework (TDF) will be used to assess nurses' behaviours related to implementation of enteral feeding algorithms being assessed during the volume-based EN RCT⁴⁸.

Sample: Bedside nurses who participated in the volume-based EN RCT. Phenomenon of interest: nurses' perception and experiences of the implementation of the volume-based EN algorithm.

Design: Mixed methods Case-study. Evaluation: Deductive analysis.

Methods: Quantitative: During the volume-based RCT the study Research Assistant will monitor nursing adherence to the volume-based EN algorithm. Data collection: This has been described within the volume-Based EN RCT methods section. Analysis: Deviations from the Volume-based EN algorithm will be reported as mean daily percent and mean percent of total study time.

Qualitative: Qualitative methods will be used to assess bedside nurses' perception and experiences of implementing the volume-based EN algorithm. Nurses will be selected through purposive sampling of bedside nurses of patients enrolled in both arms of the volume-based EN RCT. Purposive sampling will be used to ensure nurses who worked primarily day shifts, evening shifts and weekend shifts are included to assess if there is a difference in results based on the presence of the Study Coordinator on weekday shifts versus no Study Coordinator on evening/weekend shifts. Nurses will be asked about years of experience and purposive sampling will allow for a range of nursing experience to be explored. Face-to-face or zoom semi-structured interviews will be conducted. Interviews will be recorded for data analysis. A minimum sample size for interviews set a-priori will be 10, with additional interviews until saturation of themes has been reached⁴⁸. Data collection will be stopped once saturation of themes has been reached. Deductive analysis will be conducted from recorded interviews by two independent reviewers. A coding guideline, based on Theoretical Domains Framework will be developed in tandem with the interview schedule and iteratively updated during data collection. Two researchers will code in duplicate into theoretical domains following the coding guideline. Reliability between the two coders will be assessed via a kappa statistic across all domains⁴⁸.

Part E: Impact and Knowledge Translation

We have included key stakeholders throughout our study design process. Stakeholders currently involved include Pediatric Intensive Care Unit (PICU) physicians, nurse practitioners, nurses, nurse educators, dietitians, the PICU research committee, the Alberta Children's Hospital Parent Advisory Committee, and Alberta Health Services. We will involve key PICU stakeholders in designing the volume-based enteral nutrition (EN) algorithm and study protocol and education plan. We have received letters of support from Provincial Practice Leaders within Alberta Health Services, Nutrition Services Management at ACH, and the ACH Research Committee including the Pediatric Critical Care section Chief. We will bring this study protocol to the ACH parent advisory committee to obtain family and child perspectives prior to implementation and once results are available.

Our primary target audience includes researchers in pediatric critical care nutrition support, national partners including the Canadian Pediatric Society Nutrition Committee, and international guideline organizations including American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society of Pediatric and Neonatal Intensive Care (ESPNIC). We are exploring collaboration with PICU nutrition colleagues from international PICU in Boston and members of the Canadian Pediatric Society.

Early engagement with stakeholders will allow streamlined knowledge translation of study results. Study results will be communicated to stakeholders, providers, and families to educate and build early support for changes in practice guidelines which may result from future research. Results of the systematic review and the feasibility study will be published in nutrition support or critical care journals, results of the mixed methods study will be published in an implementation science journal. All study results will be disseminated locally and provincially at child health and PICU meetings, and nationally/internationally by attending nutrition support and critical care conferences including the ASPEN Nutrition Science and Practice Conference.

This proposed research program including a systematic review, randomized feasibility trial, and qualitative assessment of algorithm implementation, will provide evidence to inform whether a larger scale RCT assessing the impact of a volume-based EN algorithm on reducing energy and protein deficits during PICU admission and its influence on hospital outcomes for critically ill children. The mixed methods study will provide valuable qualitative findings regarding the success of execution of our feeding algorithm that will inform future implementation within PICUs. Findings will inform larger trials powered to assess the impact of volume based EN on specific clinical outcomes of importance and will support the development and implementation of volume based EN algorithms within PICUs. Ultimately, we hope that by improving nutrition delivery during PICU admission we can improve clinical outcomes, optimize growth and development, and improve quality of life for critically ill children.

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