STATISTICAL ANALYSIS FOR THE NEED TRIAL (effectiveNess of feEding protocol on nutritional thErapy and clinical outcomes in critically ill patients: a multi-centered, cluster-ranDomized, parallel-controlled trial)

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BRIEF BACKGROUND

1 Introduction

China has one of the largest populations of critically ill patients, causing a great burden on the healthcare system, and the clinical practice of EN feeding varies massively [1-2]. A small study has shown that EN feeding protocol could improve the proportion of EN from 32% to 78% after implementing EN feeding protocol for 7 days [3]. However, to the best of our knowledge, there is a lack of large-scale data on the practice of enteral nutrition in Chinese ICUs. Our earlier cross-sectional study showed that the proportions of subjects starting EN within 24, 48 and 72 h after ICU entry was 24.8% (84/352), 32.7% (150/459) and 40.0% (200/541), respectively, suggesting the suboptimal implementation of the current guidelines [4]. Therefore we conducted this multi-center cluster-randomized study to assess the effect of a feeding protocol derived from the latest guidelines in a group of Chinese ICUs. For a protocol study, cluster-randomized method can effectively control the confounding factors across groups to obtain more reliable conclusions [5]. In addition, patient-level randomization would inevitably lead to pollution effect as the feeding protocol in the study group would always affect the clinical practice in the controls [6]. Randomization at the ICU level and stratification before randomization could help avoid pollution and between-group imbalance.

2 Development of the feeding protocol

According to the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), ESICM clinical practice guidelines and Surviving Sepsis Campaign guidelines, we developed an evidence-based feeding protocol for critically ill patients and expected to improve patient outcomes with it [7-9]. The ACCEPT trial has demonstrated that evidence-based algorithms for critically ill patient could improve the provision of nutritional support, reduce hospital stay and may decrease the hospital mortality rate [10]. Conversely, two other cluster-randomized trials have indicated that implementation of feeding strategy could provide more and earlier energy supply, but did not improve clinical outcomes [11-12]. However, controversy remains due to lack of large-scale adequately-powered randomized controlled trial in the literature. A small pilot study had shown that our feeding protocol was able to increase the proportion of EN feeding [3]. Due to the before-and-after nature of the pilot study and the limited sample size, this study was not powered enough to fully demonstrate the effect of this feeding protocol on clinical outcomes of critically ill patients, but the preliminary data it showed justified a large randomized controlled study.

3 Hypotheses to be tested

We aimed to assess the effect of a feeding protocol on nutritional therapy and clinical outcome in critically ill patients. The hypothesis is that a feeding protocol, compared to routine clinical practice, could reduce 28-day mortality in critically ill patients admitted to ICUs in China.

4 Eligibility criteria

4.1 Inclusion Criteria

1. Informed consent form obtained from the patient or next of kin;
2. 18 years old or older;

3. Within 24h of ICU admission;
4. With one or more organ failure(SOFA for any single organ system≥2);
5. Expected to stay in ICU for more than seven days;
6. Oral diet is not likely to be restored within three days.

4.2 Exclusion Criteria

1. Patients received EN in the past three days;
2. Patients receiving palliative treatment or expected to die within 48 hours;
3. Women in pregnancy;
4. Long-term use of steroids or immunosuppressive agents;
5. Patients with malignant diseases receiving radiotherapy or chemotherapy.

5 Randomization

The R language was used for randomization in this study. All the participating centers were stratified according to the nature of the hospital (regional and tertiary) and type of ICU (emergency, medical, surgical, and others). Randomization occurred in a 1:1 fashion for the participating centers within the same category with computer-generated random numbers. Allocation concealment was maintained by conducting randomization after consent to participate was obtained.

A web-based electrical database was used for data collection and storage. All data was input by the primary investigator or nominated investigator (two or fewer nominated investigators for each participating center) approved by the primary investigator. Training for data entry was performed by the developer web database and training for conduct of the study was conducted by the Sponsor of the NEED trial.

6 Intervention arm

Before EN initiation, hemodynamic parameters should be stabilized evidenced by MAP≥65 mmHg and lactate<4mmol/L, with decreasing vasoactive dose. The gastrointestinal function will be then evaluated with the acute gastrointestinal injury (AGI) grading system. For patients with AGI of I, EN will be started at 25 ml/h. For

patients with AGI II-III, predigested EN will be started at 10–15 ml/h. EN should be withheld for those with AGI IV. If patients are at high risk of malnutrition based on the Nutric score ≥5 (IL-6 not included), but EN cannot be initiated, PN should be started. Otherwise, PN will be withheld for 7–10 days. Patients on EN will be evaluated using tolerance score for every 4-6 hours. Feeding protocol and the tolerance score are shown in Figure 1 and Table 1, respectively. EN will be discontinued when EN tolerance score is greater than 5 points. Adverse events will be treated and managed with standardized protocol (Fig 2) by the treating team. In detail, EN will be discontinued in the presence of persistent abdominal pain. Physical examination and abdominal computed tomography will be ordered if deemed necessary by the treating team, and if there are signs of bowel obstruction and/or ischemia, EN should be discontinued immediately. Diarrhea can be caused by enteral feeding, specific diseases and drugs, and infections, which should be considered and diagnosed by the treating team. If Clostridium difficile infection is identified, the patient will be treated with metronidazole or vancomycin.

Figure 1: Feeding Protocol

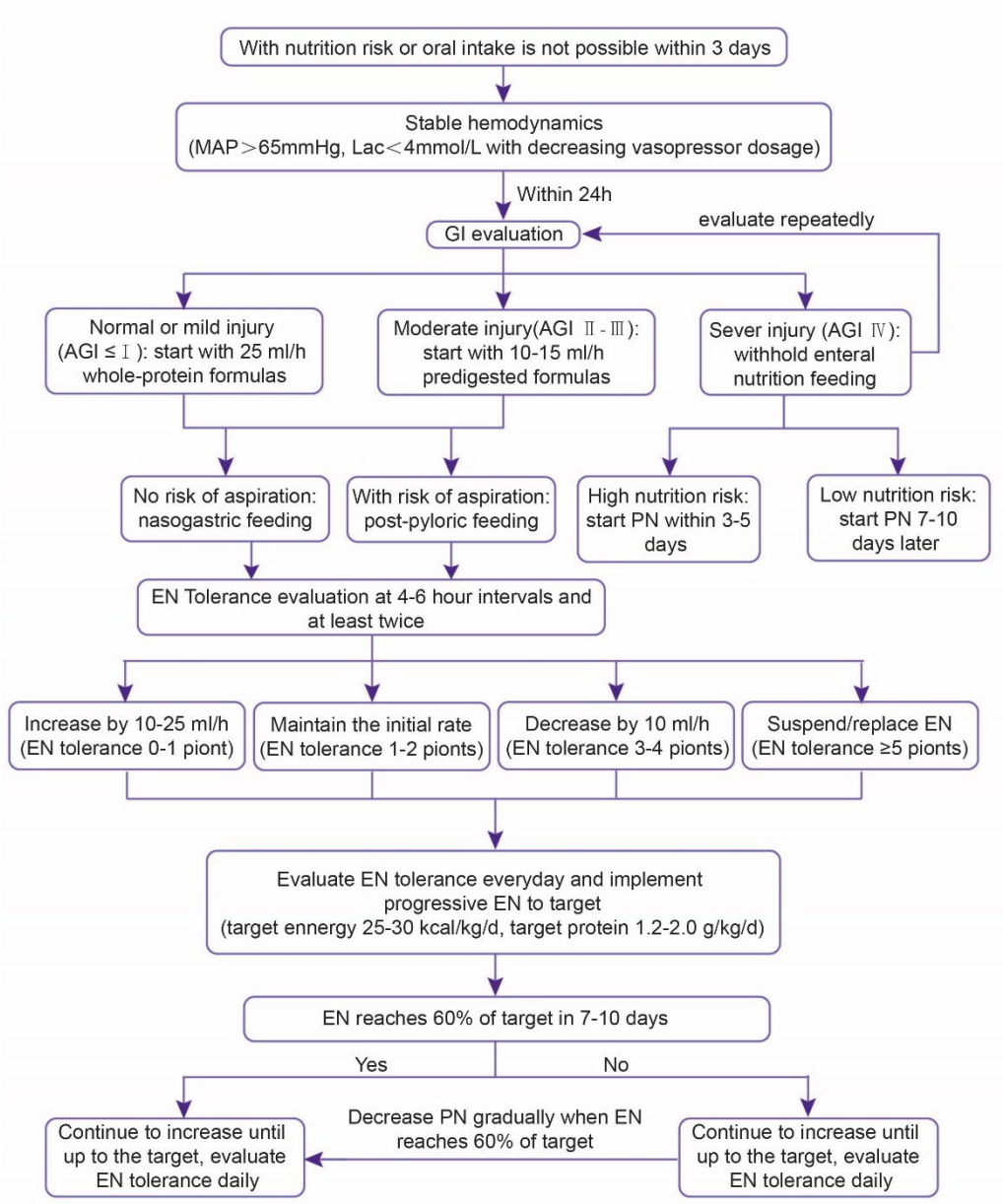
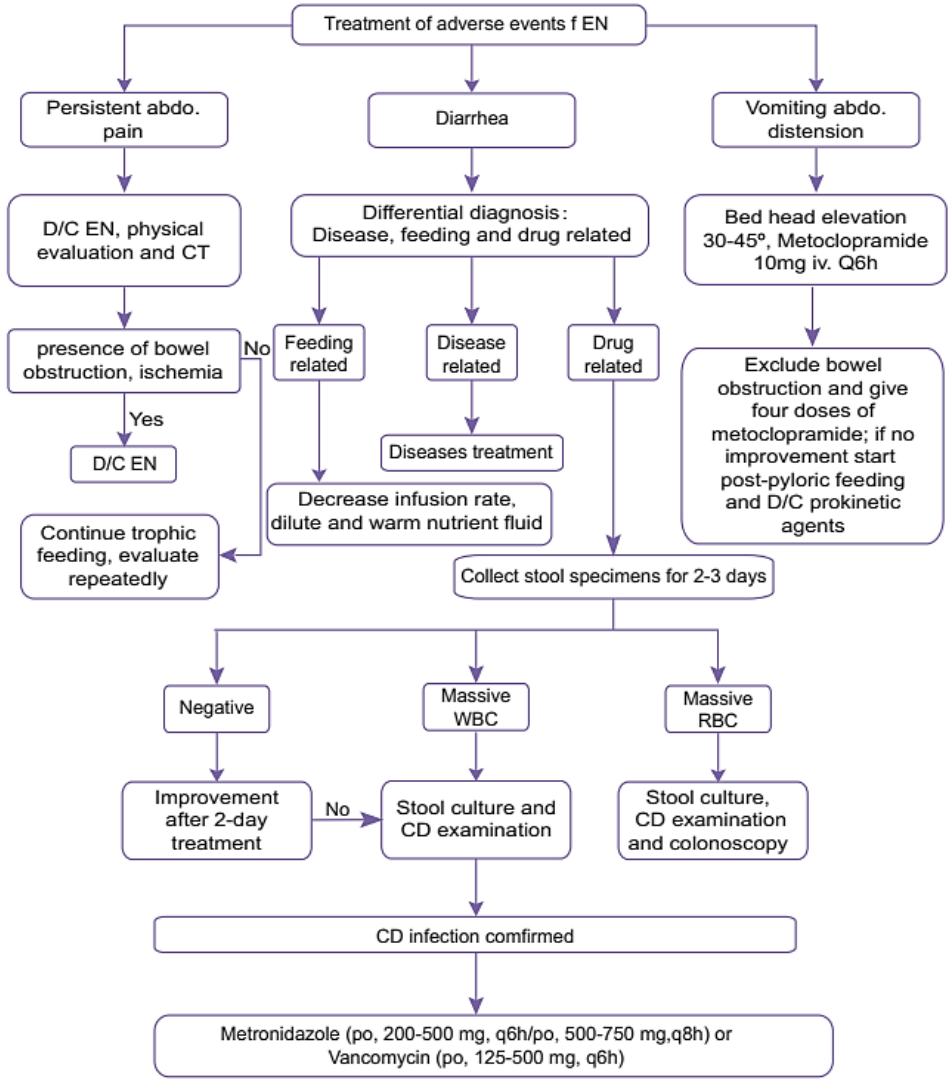


Table 1: EN tolerance Score

Points	0	1	2	5
Abdominal distension/pain	None	Mild distension; no distension	Moderate distension; IAP 15~20mmHg; spontaneous resolution of abdominal pain	Severe distension; IAP>20mmHg; No spontaneous resolution of abdominal pain
Nausea/vomiting	None; continuous gastric	Nausea but no vomiting	Nausea and vomiting without need for	Vomiting requiring gastric

	decompression without symptom		decompression; 250ml<GRV<500ml	decompression; GRV>500ml
Diarrhea	None	Loose stools 3-4 times/day with volume <500ml	Loose stools ≧5 times/day with a volume between 500-1500ml	Loose stools ≧ 5 times/day with volume≧ 1500ml

Figure2: Protocols for the management of adverse events



6.2 Control group

All the participants in this group will be treated without any change to current clinical practice. No adherence to uniform protocol or guidelines will be required for the study period.

6.3 General management

All patients would be cared for by the local treating team in each participating ICU, including monitor of vital signs, harvesting necessary blood samples for laboratory measurement, fluid therapy, and so on. In the control group, nutritional therapy would be implemented routinely in each participating ICU. All co-interventions will be left to the discretion of the treating clinical teams and recorded in the patient's medical record.

7 Data collection and follow up

7.1 Data collection

All the data that is necessary to define baseline patient characteristics, the implementation of the feeding protocol and control therapies, potential confounding co-interventions, and outcomes will be collected.

The primary investigator of each center will be responsible for enrollment of patients and data input. A group of statistician will be accountable for pre-definition of statistical analysis and subgroup analysis.

A web-based electrical database will be used for data collection and storage. All data will be input by the primary investigator or nominated investigator(less than two for each participating center) approved by the primary investigator. Training for data entry will be performed by the supplier of the electrical database and the sponsor of the NEED trial.

7.2 Follow up

All patients recruited will be followed until either 28 day after enrollment or death, depending on which comes first. Follow-up will be restricted to information regarding the vital status and other related study clinical outcomes. Follow-up will be conducted

by study staff by either direct contact with the patient or their NOK. Patients who withdraw from the study for any reason will also be followed up according to the study follow-up schedule and analyzed on an intention-to-treat principle.

8 Outcome measures

8.1 Primary outcome measures

The primary outcome measure is all-cause mortality at day 28 after randomization (the day of randomization will be set as day 1).

8.2 Secondary outcome measures

8.2.1 Process measures

1. Time to start EN
2. Time to start PN
3. Mean nutrition support days within first 7 days after enrollment
   3.1 Mean nutritional support(either EN or PN or both) days within first 7 days after Enrollment
   3.2 Mean EN support days within first 7 days after enrollment
   3.3 Mean PN support days within first 7 days after enrollment
4. Target-reaching rate of EN on day3 and day7 after enrollment
5. EN tolerance score in first 7days after Enrollment
6. Days requiring prokinetic agents within first 7 days after enrollment
7. Proportion of patients receiving PN prescription with first 7 days after enrollment
8. Mean energy per day over first 7 days for patients who were fed
9. Proportion of patients never fed during the first 7 days after enrollment
10. Proportion of patients fed within 24 h after enrollment
11. Mean energy delivered for patients who were fed within first 7 days after enrollment
   11.1 Mean energy delivered from EN within first 7 days after enrollment
   11.2 Mean energy delivered from PN within first 7 days after enrollment
12. Proportion of patients who received a post-pyloric feeding tube (patients receiving

EN) within first 7 days after enrollment.

8.2.2 Organ dysfunction-related outcomes

1.New onset organ failure within first 7 days
  1.1 New-onset respiratory failure;
  1.2 New-onset cardiovascular failure;
  1.3 New-onset renal failure
2. New receipt of organ support therapy within first 7 days
  2.1 New receipt of mechanical ventilation (non-invasive included)
  2.2 New receipt of renal replacement therapy
  2.3 New receipt of vasoactive agents
  2.4 Days requiring CRRT within first 7 days after enrollment
  2.5 Days requiring insulin within first 7 days after enrollment
  2.6 Days requiring MV within first 7 days after enrollment

8.2.3 Additional outcomes

1. Incidence of secondary infection in ICU
2. Length of ICU stay

8.3 Definition of outcomes

New- onset organ failure: organ failure occurring during first 7 days and not present at enrollment. Organ failure is defined as an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more for each organ system(Respiration, Cardiovascular, Renal).

New receipt of organ support therapy: requirement of organ support therapy (mechanical ventilation, renal replacement therapy and vasoactive agents) not applied at enrollment.

All-cause mortality at day 28: defined as patient vital status (alive/dead) to be determined on the 28th calendar day post-enrollment (the day of randomization will be set as day1).

STATISTICAL ANALYSIS

9 Data and safety monitoring board

Data and safety monitoring board (DSMB) was composed of an independent group of experts that offered advice during the implementation of the study. The DSMB can recommend that a trial should be stopped early because of concerns about participant safety or because the main research question has been answered.

At study mid-recruitment, the DSMB met on 9th Feb 2019 after enrollment of 1727 patients and determined that the stopping rules were not met and that the trial should continue.

10 Sample size and power

The planned sample size was 2250 participants, corresponding to a target sample size of 25 eligible participants per ICU (cluster) for 90 ICUs (clusters). According to previous studies, 28-day mortality for mixed ICU patients was demonstrated to be 20%, which was used as the event rate in the control group. The Nutrition protocol was assumed to be able to reduce the mortality rate to 12% [10]. The type I error was 0.05, and the statistical power was 80%. The inter-class correlation was 0.1. A total of 90 centers with 25 subjects in each center were required to meet the statistical power. Sample size calculation was performed by using the CRTSize package. The full code for the calculation was: n4props (pe=0.12, pc=0.20, m=25, ICC=0.10, AR=1, alpha=0.05, power=0.80)

11 The flow of ICUs and patients

The flow of ICUs and patients through the trial will be reported in accordance with the CONSORT extension statement for cluster trials (Fig. 1). The flow diagram will include the number of eligible and recruited centers, the number of eligible and recruited patients and then, by allocated group, the number of patients who continued through the trial, the number of withdrawing, the number of data missing and the

numbers included in the analysis.

12 Withdrawals

In ICUs allocated to the intervention group, patients or their next of kin could choose to opt out from participating in the collection of outcome measures, while remaining under the intervention if appropriate. Patients who discontinued completing the data collection prior to the end of the trial period will still be included in the full analysis population unless they requested otherwise. Reasons for withdrawal should be documented wherever possible.

13 Basic principles of analysis

The reporting and presentation of this trial will be following the CONSORT guidelines for cluster-randomized trials [13], with the primary comparative analysis being conducted on an intention-to-treat basis.

Descriptive statistics will be used to assess any marked baseline differences in demographics or outcome measures between the two groups, taking clustering into account. Comparisons of binary outcomes will be expressed as odds ratios with 95% confidence intervals and comparisons of continuous outcomes as mean differences together with 95% confidence intervals. Between-group comparisons will be made using generalized linear mixed-model (weighted by clusters). Additional analysis will be performed taking account of the hierarchical nature of the study design as well as important cluster level baseline covariates (bed number, ICU type, teaching/community) and baseline individual level covariates (where relevant).

All analyses will account for clustering to ensure correct type I error rates and confidence intervals. Our cluster-randomized trial will be analyzed on the individual level, and use generalized linear mixed-model to account for clustering among patients in the same cluster. In addition, a sensitive analysis will be undertaken without considering effects of clustering to ascertain whether the submodels significantly influenced the results of the primary effectiveness analysis, exploring the robustness and accuracy of the primary conclusions.

Based on the principle of intention to treat (ITT), full-analysis set (FAS) will be performed on all the randomized population. FAS will be used for the analysis of baseline characteristics and main therapeutic interventions

Two-sided 5% significance levels will be used to identify statistically significant results. A two-sided 10% significance level will be used to identify results that are trending towards statistical significance. All confidence intervals reported will be 95% confidence intervals. All p-values and estimates of change will be calculated at the individual level.

14 Unadjusted analysis and adjusted analyses

All comparative analyses will allow for the clustered nature of the data to ensure correct confidence intervals and type I error rates are calculated [14-16]. As the trial includes a reasonable number of clusters (i.e., 90 ICUs), the analyses will be based on the individual patient-level data, allowing for the clustering between patients within the same ICU, rather than on the cluster-level summarized data, which is appropriate when only a small number of clusters are present [14]. For each outcome, unless otherwise specified, the primary analysis will be the unadjusted analysis taking effects of clustering into account.

An objective pre-specified algorithm will be used to select variables for inclusion in additional covariate adjusted analysis, with the statistical models including the three stratification variables (bed number, ICU type, teaching/community) and baseline values for the outcomes under consideration. The results of the adjusted analysis will also be presented for completeness.

15 Presentation of comparative analyses

For each of the continuous outcomes, the mean and standard deviation for each allocated group will be presented, together with the mean between-group difference, 95% confidence interval for the difference and p value. For binary outcomes, the percentage and frequency of patients in the outcome category of interest (e.g.,

percentage of secondary infection) will be presented for each allocated group, along with the odds ratio for the intervention effect, 95% confidence interval for the odds ratio and p value. Besides, the intra-cluster correlation coefficient will be reported for each outcome, based on the unadjusted analyses, together with a 95% confidence interval.

16 Analysis of primary outcome

The primary conclusions of this project will be based on analyses conducted under the principle of intention to treat (ITT). Comparisons between the two groups will be implemented using generalized linear mixed-model, allowing for the clustered nature of the data (see 'Unadjusted and adjusted analyses' section above).

17 Analysis of secondary outcomes

We consider all secondary analyses to be exploratory and hypothesis-generating and therefore do not adjust for multiple comparisons. Secondary outcomes based on count data were analyzed using a Poisson model. Baseline balance of proportions will be assessed using a χ^2 test, and continuous variables are assessed using t tests. All analyses will be appropriately adjusted for the effects of clustering.

If the results of the covariate adjusted analysis of the primary outcome differ in any meaningful way from the results of the unadjusted analysis of the primary outcome with regards to statistical significance thresholds or estimation of the magnitude of treatment effect, unique covariate adjusted models will be developed for each secondary outcome, using random-effects regression, allowing for the clustered nature of the data and including the stratification factors (bed number, ICU type, teaching/community) and baseline values of the variable under consideration.

The following are baseline variables ascertained at the time of enrollment: Age, Gender, Weight, BMI (as a continuous variable *and* categorized into underweight [BMI < 18.5kg/m^2] and obese [BMI ≥ 30 kg/m^2]), APACHE II score, NUTRIC score, SOFA score, Ramsay score, Proportion of infectious patients within first 7 days, confirmed infection site (Pulmonary, Urinary tract, Abdominal cavity, Blood, Catheter,

Intracranial, Others), Source of admission (Emergency department, Surgical department, Medical department, Other hospital, others), Surgical admission type (Elective, Emergency), Comorbidities (Hypertension, Coronary disease, Insulin dependent Type I or II diabetes, Chronic Respiratory diseases, Stroke, Gastrointestinal disease, Malignant tumor, others), Admission diagnosis (Cardiovascular, Respiratory, Trauma, Post-CPR, Neurological, End-stage disease, Metabolic, Perioperative, Sepsis, others), current status of organ failure (respiration, renal and cardiovascular described by individual SOFA score), current therapy for sedation and analgesia(Ramsay score), current status of infection (site, culture results and date of diagnosis) and gastrointestinal function (described by AGI score).

18 Missing primary outcomes

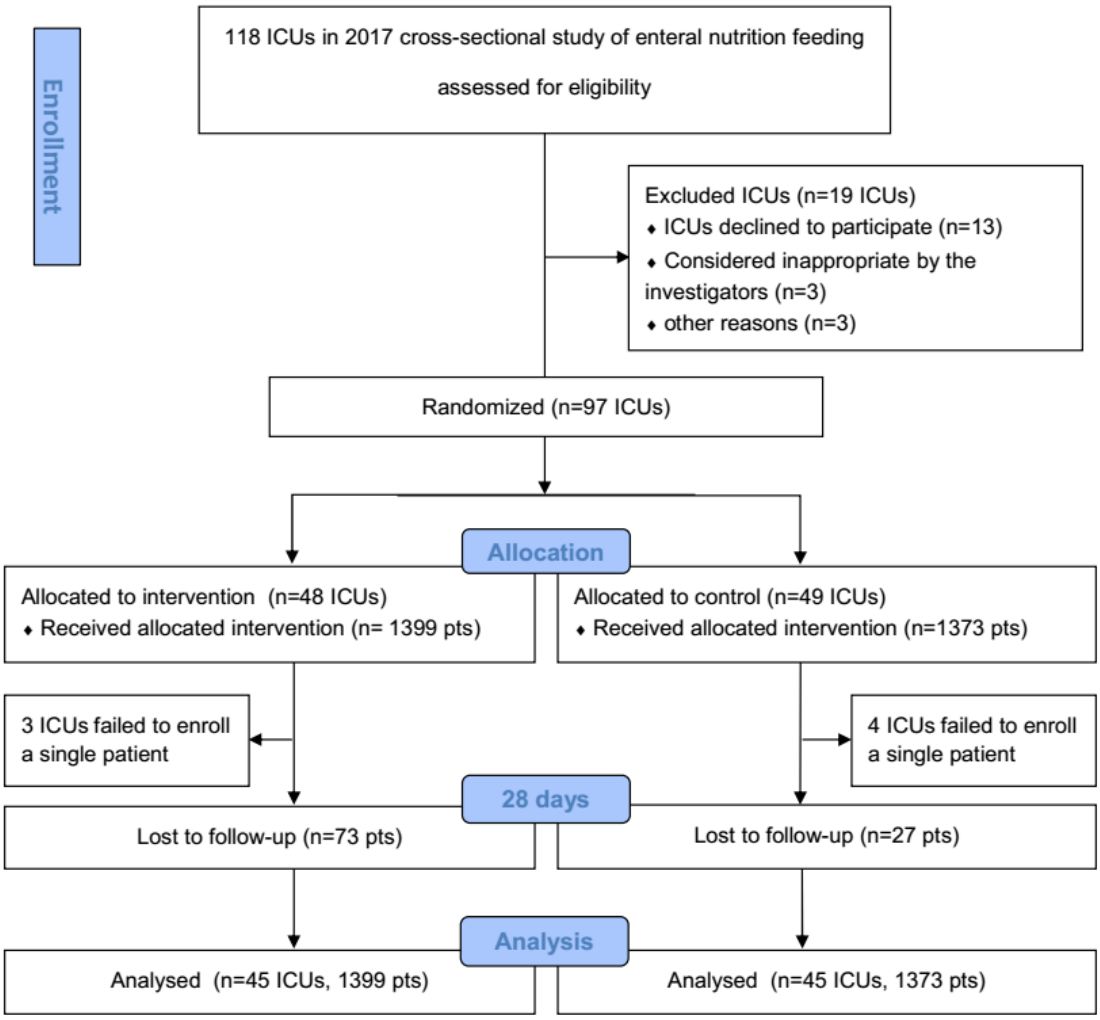
Missing primary outcomes (Day 28 vital status) will be assumed to be missing at random (MAR) and thus will be 'ignored' in the primary analysis. However, if greater than 5% of all primary outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.

19 Missing baseline prognostic variables

Missing baseline prognostic variables will be replaced with mean values calculated from the observed non-missing instances of that baseline prognostic variable. The imputed means will be calculated using pooled data from both arms. Imputed means will *not* be calculated within the treatment arm using treatment arm-specific data *nor* will any post-randomization information be incorporated into the calculation. Furthermore, replacement values for missing calculated constructs such as BMI and APACHE II score will be estimated using non-missing component-level information. For example, if one of the components of BMI is missing, such as height, overall mean height will be imputed, and BMI will be calculated with the known weight and imputed mean height.

If a baseline prognostic variable requires imputation of missing values, the percent of cases that were originally missing will be reported.

Fig. 1 Flow of ICUs and patients through the NEED trial



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