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Protocol

Optimal delivery of enteral protein in the critically ill: A protocol for a systematic review and meta-analysis of randomised controlled trials

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SUMMARY

Background: The optimal dose of enteral protein to deliver during critical illness remains uncertain. International clinical practice guidelines recommend protein targets ranging from 1.2 to 2.0 g/kg body weight/day, which is greater than the amount recommended in health. This protocol details the conduct of a systematic review and meta-analysis to evaluate the effect of enteral protein delivered within the international recommended guidelines (1.2–2.0 g/kg/day) compared to less than international recommended guidelines (<1.2 g/kg/day) on mortality and morbidity outcomes.

Methods: A systematic review and meta-analysis will be undertaken in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive literature search of studies indexed in MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials will be conducted. Studies will be included if they are randomised controlled trials (RCTs) enrolling adult critically ill patients comparing predominately enteral protein delivery with one arm receiving 1.2–2.0 g/kg/day protein/kg/day ('greater protein') and another arm receiving <1.2 g protein/kg/day ('lesser protein'). Two independent reviewers will perform title and full text screening for study inclusion, extract data from included studies, and assess study quality using the Cochrane Risk of Bias 2 tool. The primary outcome will be mortality at 90 days. Secondary outcomes will be clinical (infectious complications, and durations of ICU and hospital stays and mechanical ventilation), patient-centred (discharge destination, physical function and quality of life) and muscle (muscle mass, strength) outcomes.

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Results: Random-effects meta-analysis will be fitted for all outcomes, and, for the primary outcome, risk ratios will be pooled using a random-effects meta-analysis model and pooled treatment effect presented as risk ratio (95% Confidence Interval).
Conclusions: This systematic review and meta-analysis will compile data to determine whether outcomes are optimised with greater or lesser amounts of enteral protein delivered during critical illness.
Systematic review registration: CRD42025547923.

1. Introduction

1.1. Rationale

Rapid and substantial muscle wasting occurs during critical illness, with patients losing almost 20% of muscle mass in the first 10 days of an intensive care unit (ICU) admission [1,2]. This muscle wasting is a major contributor to 'ICU-acquired weakness' [3], which is associated acutely with increased mortality, slower weaning from ventilator support, longer time to discharge alive from ICU and hospital, and higher in-hospital costs [4–6]. The detrimental effects of ICU-acquired weakness persist after hospital discharge, and adversely affect physical function and health-related quality of life [7–9]. Critically ill patients who receive organ support predominately receive protein via enteral nutrition (EN) [10], providing a potential therapeutic intervention for exploration.

It has been suggested that augmenting dietary protein doses in critical illness has potential to attenuate muscle loss and improve patient recovery, with recent large-scale randomised controlled trials (RCTs) conducted on this topic [11,12]. International clinical practice guidelines have recommended a broad range of daily protein targets: the American Society of Parenteral and Enteral Nutrition (ASPEN) recommend 1.2–2.0 g/kg body weight/day [13], while the European Society of Clinical Nutrition and Metabolism (ESPEN) recommend 1.3 g/kg body weight/day delivered progressively [14].

Since 2012, eight systematic reviews evaluating protein delivery in the critically ill have been published [15–22], with seven including a meta-analysis [16–22]. The previous systematic reviews and meta-analyses are summarised in the supplementary material. In summary, these reviews concluded that delivery of augmented protein doses during critical illness has no impact on mortality at any timepoint, or length of ICU or hospital stay. Uncertainty remains for patients with an acute kidney injury. However, using a Bayesian approach, one of the most recent reviews by Heuts et al. (22 RCTs; 4164 patients) concluded a considerable probability of an increased mortality risk with higher protein delivery (The probabilities of a 1%, 2.5%, 5%, and 10% increase in mortality by higher protein delivery were 51.5%, 44.3%, 32.4%, and 10.3%, respectively) [22]. Three of the 8 reviews compared protein doses within international recommendations (≥1.2 g/kg/day) to below recommendations (<1.2 g/kg/day; representative of usual care) [17,20,21]. However, of these reviews, only Fetterplace et al., in 2020 compared protein doses delivered via the enteral route only [17].

Since the latest meta-analysis, two large randomised clinical trials have been conducted which will provide additional data with the capacity to impact conclusions from previous analyses. The PRECISe trial randomised 935 patients to standard or high enteral protein doses and reported that high enteral protein provision resulted in worse health-related quality of life at 180 days compared with standard protein provision (mean difference −0·05 (95% CI −0·10 to −0·01; p = 0·031) [12]. In addition, there was no difference in mortality (secondary outcome) at any point during the 180 day follow up high protein compared to standard protein (hazard ratio 1·14, 95% CI 0·92 to 1·40; p = 0·22). The recently completed TARGET Protein trial enrolled over 3000 patients into a cluster randomised, double cross-over clinical trial evaluating augmented enteral protein administration compared to usual protein [23]. Taken together, this will more than double the number of patients enrolled from the existing largest systematic review and meta-analysis evaluating protein delivery. The TARGET Protein data will be published by co-authors of the proposed systematic review and meta-analysis and will be incorporated to provide the most updated evidence. The proposed systematic review will also evaluate certainty of evidence and the credibility of heterogeneity of effect.

1.2. Objective

To perform a systematic review and meta-analysis of RCTs in critically ill adults evaluating the effect of protein delivered predominantly via the enteral route achieving doses within the ASPEN and ESPEN international recommended guidelines (1.2–2.0 g/kg/day; 'greater protein' group), compared to enteral protein delivered below these international recommended guidelines (<1.2 g/kg/day; 'lesser protein' group) on mortality, and clinical, patient-centred, and muscle outcomes.

1.3. Aims

1.3.1. Primary

To determine if delivery of enteral protein doses within international recommended guidelines (1.2–2.0 g/kg/day); 'greater protein' group) when compared to lesser protein (<1.2 g/kg/day) reduces mortality in critically ill adults.

1.3.2. Secondary

To determine if delivery of enteral protein doses within international recommended guidelines (1.2–2.0 g/kg/day) when compared to lesser protein (<1.2 g/kg/day) is associated with reduced morbidity as determined by:

- Improved clinical outcomes – defined as reduced infectious complication, duration of mechanical ventilation, and length of ICU and hospital stay.
- Improved patient-centred outcomes – defined as improved physical function, more favourable discharge destination, and better quality of life scores.
- Improved muscle outcomes – defined as greater muscle mass or strength, or greater attenuation of muscle mass loss or strength.

2. Methods

2.1. Design

A systematic review and meta-analysis of RCTs will be conducted and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [24] and in adherence with the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [25]. In addition, this protocol has been prepared in adherence with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines [26] (supplementary material). This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42025547923.

2.2. Eligibility criteria

Studies will be assessed for eligibility against the below inclusion criteria:

- RCT.
- Designed to include only adult patients as defined by the primary publication.
- Included critically ill patients– defined as patients treated in an ICU environment e.g. mechanically ventilated, or if this is unable to be ascertained, then a mortality of >5% in the control group [19].
- Compared protein doses predominately delivered via EN – 'predominant EN' is defined as studies that provided nutrition therapy via the enteral route in preference to parenteral nutrition (PN) [17]. Studies will be included if supplemental PN was administered.
- One arm received a mean of 1.2–2.0 g protein/kg/day ('greater protein'), and another arm received <1.2 g protein/kg/day ('lesser protein').
- Reported similar overall mean energy delivery between groups.
- Reported mortality and/or a clinical, patient-centred, and/or muscle outcome suitable for contribution to one or more of the primary or secondary aims of the meta-analysis.

2.3. Studies will be assessed against the below exclusion criteria:

- Different protein doses delivered were secondary to the delivery of specific amino acid/s or their metabolites e.g. glutamine, arginine, or hydroxymethylbutyrate (HMB) supplementation.
- Predominately (>50%) elective surgery patients were included.
- Only biochemical, metabolic, or nutritional outcomes were reported.

2.4. Intervention and comparators

The intervention group will comprise study arms which report a mean protein delivery of 1.2–2.0 g/kg/day – within the international recommended guidelines. The comparator group will compromise study arms which report a mean protein delivery of <1.2 g/kg/day – less than international recommended guidelines [13,14].

3. Outcomes

Outcomes that will be reported are included in Box 1.

Box 1
Outcome measures

Primary outcome

The effect of greater enteral protein delivery (within the international recommended guidelines 1.2–2.0 g/kg/day) compared to lesser enteral protein (less than international recommended guidelines <1.2 g/kg/day) on:

- Mortality at 90 days. Note that if a study does not report 90 day mortality, the nearest timepoint will be reported in the following order: 60 day mortality, 28 day mortality, 180 day mortality, hospital mortality, and ICU mortality

Secondary outcomes

The effect of greater enteral protein delivery (within the international recommended guidelines 1.2–2.0 g/kg/day) compared to lesser enteral protein (less than international recommended guidelines <1.2 g/kg/day) on:

- Infectious complications – defined as any mention of infection of any severity as an outcome of, or acquired complication during the original trial
- Duration of ICU admission
- Duration of hospital admission
- Duration of mechanical ventilation
- Muscle mass at any timepoint – assessed using ultrasound imaging of any muscle e.g. quadriceps muscle layer thickness, or any other validated technique e.g. dual-energy x-ray absorptiometry (DEXA) or computed tomography (CT)
- Muscle strength at any timepoint – assessed using handgrip dynamometry or any other validated technique. Hand grip dynamometry at ICU discharge will be given preference
- Physical function at any timepoint – assessed using 6-min walk test, gait speed, or any other validated technique
- Quality of life at 90 days – assessed using a validated quality of life questionnaire e.g. 36-item short form survey (SF-36), EuroQoL 5-Dimension 5-level health utility score (EQ-5D-5L), RAND 36-item health survey (RAND-36), or quality of life in neurological Disorder (Neuro-QoL). If a study does not report 90 day quality of life, the nearest timepoint will be reported in the following order: 60 days, 28 days, 180 days. EQ-5D-5L will be given preference.
- Discharged to rehabilitation facility

Abbreviations: ICU = internsive care unit.

3.1. Information sources

The following databases will be searched: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Ovid, Excerpta Medica Database (EMBASE) via Ovid, Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCOhost, and Cochrane Central Register of Controlled Trials (CENTRAL). Databases will be searched from inception to the final data search cutoff date. In addition, reference lists from relevant reviews and clinical guidelines will be checked to ensure all relevant trials are included. Advice has been sought from a senior librarian with experience and knowledge in medical systematic reviews to develop a search strategy for each database. The search will be repeated prior to submission if the time between the search date and submission for publication exceeds six months.

3.2. Search strategy

A logic grid was developed with the identification of four major concepts: 1) critical illness, 2) EN support, 3) dietary protein, and 4) RCT. To enhance the search, synonyms were added, and major database subject headings/controlled vocabularies used (MEDLINE – Medical Subject Headings; EMBASE – Emtree; CINAHL – CINAHL Subject Headings; CENTRAL – Medical Subject Headings). In addition, phrase searching (multiple words searched side-by-side in that exact order), truncation searching (words with alternative endings, such as plural versions), wildcards searching (spelling variations, such as British versus American), proximity operators searching (words within a certain range from other words), and frequency operators searching (for words that appear at least a set number of times in a resource) will be conducted. Supplementary material shows the proposed search strategy for MEDLINE.

3.3. Selection process

Search results will be collated using Covidence (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org), with study selection completed in stages described below.

3.3.1. Stage 1: removal of duplicates

Duplicate articles will be removed on upload to Covidence.

3.3.2. Stage 2: screening of titles and abstracts

Two authors (any combination of MJS, JLMB, or LSC) will independently assess titles and abstracts against the eligibility criteria. Discrepancies will be resolved in conjunction with the third author (MJS, JLMB, or LSC). Where relevance of the study is unclear, the record will pass to Stage 3.

3.3.3. Stage 3: screening of full text articles

Following full text retrieval, two authors (MJS and JLMB) will independently screen full text articles against eligibility criteria. Discrepancies will be resolved in conjunction with a third author (LSC).

3.3.4. Stage 4: screening of reference lists

Two authors (MJS and JLMB) will independently screen the reference lists of full text articles that meet eligibility criteria and previous systematic reviews [15–19] to further identify eligible articles not identified in the original search. Discrepancies will be resolved in conjunction with a third author (LSC).

3.4. Data extraction

Data from included trials will be extracted and entered into a pre-defined data extraction form (Microsoft Excel) independently by two authors (MJS and JLMB). Any discrepancies will be discussed between the authors at the end of the data extraction process to obtain consensus. The corresponding authors of relevant publications will be contacted via email to clarify/obtain unclear/missing data. If the author is unresponsive to the first email, a follow-up email will be sent one week following the first email. If the author remains unresponsive to the second email, no further follow-up will be made. If data requires conversion (i.e. mean (SD) to median (IRQ)) and the corresponding author remains unresponsive, no conversions will be completed, and this data point will be excluded from the meta-analysis. Any remaining discrepancies will be resolved in conjunction with a third author (LSC). Data extracted from the primary publication are listed in Box 2.

Box 2
Data extraction

Publication information:
- Surname of first author
- Year of publication
- Country/ies in which trial was conducted – if multi-centre list all countries
- Trial design
- Primary aim

Patient demographics - number (%)/mean ± SEM/mean ± SD/median (IQR) (for each arm of the trial):
- Number of participants recruited and number of participants analysed for the primary outcome
- Age of participants (years)
- Sex (Male/Female)
- Weight (kg)
- Body mass index (kg/m^2)
- Severity of illness score (Acute Physiology and Chronic Health Evaluation (APACHE II or III) or Sequential Organ Failure Assessment (SOFA) score)
- Admission type (emergency vs elective)
- Proportion of mechanically ventilated patients

Intervention - number (%)/mean ± SEM/mean ± SD/median (IQR) (for each arm of the trial):
- Time to commencement of intervention from ICU admission (hours)
- Duration of intervention (days)
- Route of intervention (EN/PN)
- Energy prescription (kcal/day or kcal/kg/day or kJ/day or kJ/kg/day)
- Protein prescription (g/day or g/kg/day)
- Energy delivery (kcal/day or kcal/kg/day or kJ/day or kJ/kg/day)
- Protein delivery (g/day or g/kg/day)
- Body weight used for protein prescription e.g. ideal body weight, actual body weight, adjusted body weight
- Carbohydrate in intervention relative to control (more, similar, less)
- Fat in intervention relative to control (more, similar, less)

Outcomes - number (%)/mean ± SEM/mean ± SD/median (IQR)/ effect estimate (for each arm of the trial):

Clinical (timepoint assessed)
- Mortality and timepoint reported
- Infectious complication events during hospitalisation after randomisation (as defined by the included trials)
- Duration of ICU admission (days)
- Duration of hospital admission (days)
- Length of mechanical ventilation (hours)/ventilator free days

Patient-centred (methods of assessment, direction of effect, and timepoint assessed)
- Quality of life
- Physical function measures (score, name of tool, direction of effect)
- Discharge to a rehabilitation facility

Muscle (methods of assessment, direction of effect, and timepoint assessed)
- Muscle mass
- Muscle strength

Abbreviations: IQR = interquatile range; kg = kilogram; kcal = kilocalories; kJ = kilojoules; m = metres; SEM = Standard error of the mean; SD = standard deviation.

3.5. Risk of bias in individual studies

Two authors (MJS and JLMB) will independently assess the risk of bias of each outcome in the included studies using the Cochrane Risk of Bias tool for randomised trials 2 (RoB 2) [27]. Any discrepancies will be discussed between authors at the end of the data extraction process to obtain consensus. The overall RoB 2 assessment will be categorised as low risk of bias, some concerns, or high risk of bias. For cluster randomised trials, the RoB 2 tool variant specifically for cluster randomised trials will be used; noting that cluster crossover trials do not have a specific variant [27].

3.6. Data synthesis

Data analyses will be undertaken using the statistical software, Stata or R. Random-effects meta-analysis will be fitted for all outcomes. Random-effects models have been chosen as the intervention is not expected to be the same across the different trials, and therefore, the effect is expected to arise from different distributions. For binary outcomes (i.e., mortality), the risk ratios will be pooled using a random-effects meta-analysis model (i.e., DerSimonian and Laird inverse variance approach), and the pooled treatment effect presented as risk ratio (95% CI). For continuous outcomes measured on different scales (i.e., muscle mass, muscle strength and quality of life), the standardised mean difference will be pooled using a random-effects model and estimate τ^2 using random-effects maximum likelihood (REML) to estimate the standardised mean difference. For continuous variables measured at baseline and at follow-up (e.g. muscle mass), the estimate obtained from an analysis of covariance (ANCOVA), where available, and post-intervention values when estimates from ANCOVA are not available, will be pooled. For the meta-analysis of outcomes measured at two timepoints, τ^2 will be estimated using REML method. Finally, for meta-analysis of outcomes with a skewed distribution, the effects will be pooled according to Higgins et al. [28,29]. For estimates arising from cluster-randomised trials or cluster cross-over trials, we will extract the effect estimate (95% CI) from an analysis that accounts for the cluster design and time trends (for cross-over trials) (e.g., from a multilevel model) and use the generic inverse-variance approach to pool the estimates.

Statistical heterogeneity and inconsistency will be measured using τ^2 and I^2 statistics. Forest plots will be presented to visualise the distribution of effects across included trials separately for each outcome. If more than 10 trials meet the eligibility criteria for a given outcome, small study effects will be assessed visually using funnel plots [30].

3.7. Certainty assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to rate the certainty of evidence for primary and secondary outcomes [31]. The certainty of evidence will be based on whether an effect (benefit or harm) exists with greater protein. Evidence from RCTs starts with high certainty but can be rated down due to the risk of bias, inconsistency, indirectness, publication bias, and imprecision [31].

3.8. Analysis of subgroups

The Credibility of Effect Modification Analyses (ICEMAN) tool will be used to assess the credibility of the subgroup effect if any are identified [32]. The following subgroup analyses will be conducted for the primary outcome only:

- Patients receiving exclusive EN versus EN plus supplemental PN to evaluate interaction between the addition of PN as a strategy to optimise protein delivery. Based on the EPaNIC results [33], the hypothesis is that increased protein via supplemental PN is harmful while increased protein with EN alone is not.
- Patients with acute kidney injury (AKI) pre-randomisation versus patients with no AKI/not known to have AKI pre-randomisation. The EFFORT Protein trial [11] suggested heterogeneity of effect in those with AKI. The PRECISe trial [12] conducted, and TARGET Protein trial [23] will conduct, within-trial subgroup analysis based on AKI. Based on published EFFORT Protein data, the hypothesis is that increased protein is harmful in those with AKI but not in those without AKI.
- Patients with higher severity of illness defined as SOFA score $\geq$9 versus patients with lower severity of illness defined as SOFA score <9 based on the results of the subgroup analysis in the EFFORT Protein trial [11].

3.9. Sensitivity analyses

The following two sensitivity analyses will be conducted:

- For the primary outcome (90 day mortality), the effect will be estimated for only those trials that reported 90 day mortality.
- For the primary outcome, the effect will be estimated for only those trials with a low risk of bias.

4. Discussion

The optimal protein dose to be delivered during critical illness to improve patient outcomes is currently unknown. This systematic review and meta-analysis will examine whether delivering enteral protein doses recommended in international clinical practice guidelines improves clinical, patient-centred, or muscle outcomes compared to lesser amounts.

This review will be limited by the definitions of morbidity outcomes that were used within the included trials, which are likely to be diverse or non-specified. It will also involve the merging of data from individual patient-randomised and cluster-randomised trials, and data obtained from open-label and blinded trial methodology. In addition, the definition of AKI and timing of its assessment may vary between trials and that subgroup may not be identified prior to randomisation in all trials [11].

The recently completed PRECISe trial will add 935 patients [12] and we are aware of the recently completed TARGET Protein trial which aimed to enrol 3000 patients in a cluster crossover desgin [23], which will significantly increase the number of patients to that included in the existing largest systematic review and meta-analysis of greater versus lesser protein doses delivered in the critically ill (4164 patients from 22 RCTs) [22].

High quality assessment tools will be used to ascertain certainty and credibility of effects. This systematic review and meta-analysis will provide clinicians with a summary of current literature and provide guidance as to whether enteral protein delivery within the international recommended guidelines (1.2–2.0 g/kg/day) or enteral protein delivery of less than international recommended guidelines (<1.2 g/kg/day) improves patient outcomes.

Author contribution:

Matthew Summers: conceptualization, writing – original draft and review and editing. **Julia Bels**: writing – original draft and review and editing. **Amalia Karahalios**: writing – original draft

and review and editing, **Jeffrey Presneill**: writing – original draft and review and editing, **Mark Plummer**: writing – original draft and review and editing. **Zheng-Yii Lee**: writing – original draft and review and editing. **Daren Heyland**: writing – original draft and review and editing, **Dieter Mesotten**: writing – original draft and review and editing. **Christian Stoppe**: writing – original draft and review and editing. **Marcel van de Poll**: writing – original draft and review and editing. **Adam Deane**: conceptualization, writing – original draft and review and editing. **Lee-anne Chapple**: conceptualization, writing – original draft and review and editing.

Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial Intelligence was not used in the writing of this manuscript.

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Declaration of competing interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2025.05.034.

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