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Use of a high protein enteral nutrition formula to increase protein delivery to critically ill patients: A randomized, blinded, parallel-group, feasibility trial

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Conflicts of interest

AMD or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study). LSC has received honoraria or project grant funding from Nutricia, Baxter, and Cardinal Health (not related to this study). EJR has unrestricted grant funding from Baxter Healthcare Corporation and has received honoraria from Nutricia Australia, and Baxter Healthcare Australia and United States (not related).

Short Running Head

Increased protein delivery to the critically ill

Abbreviations list

ABW: Actual Body Weight

BMI: Body Mass Index

IBW: Ideal Body Weight

ICU: Intensive Care Unit

EN: Enteral Nutrition

PN: Parenteral Nutrition

Clinical Relevancy Statement:

It is feasible to conduct a multi-center blinded trial with rapid recruitment of patients who received the trial enteral nutrition for a median of 8 days and clinicians blinded throughout, in

which one group receiving protein doses via the enteral route that are recommended within international guidelines and the other group receiving protein doses similar to usual care, with no signal of harm from high protein enteral nutrition.

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Abstract

Background

International guidelines recommend critically ill adults receive more protein than most usually receive. We aimed to establish the feasibility of a trial to evaluate whether feeding protein to international recommendations would improve outcomes, in which one group received protein doses representative of international guideline recommendations (high protein) and the other received doses similar to usual practice.

Methods

We conducted a prospective, randomized, blinded, parallel-group feasibility trial across six intensive care units (ICUs). Critically ill mechanically ventilated adults expected to receive enteral nutrition (EN) for ≥2 days were randomized to receive EN containing 63 or 100 g protein/liter for ≤28 days. Data are mean (standard deviation) or median [interquartile range].

Results

The recruitment rate was 0.35 (0.13) patients/day with 120 patients randomized and data available for 116 (n=58 per group). Protein delivery was greater in the high protein group (1.52 (0.52) vs 0.99 (0.27) g/kg IBW/day; difference 0.53 (95% CI 0.38 to 0.69) g/kg IBW/day), with no difference in calorie delivery (difference -26 (95% CI -190 to 137) kcal/kg IBW/day). There were no between-group differences in the duration of feeding (8.7 (7.3) vs 8.1 (6.3) days) and blinding of the intervention was confirmed. There were no differences in clinical outcomes including 90-day mortality (14/55 (26%) vs 15/56 (27%)); risk difference = -1.3 (95% CI -17.7 to 15.0) %.

Conclusion

It is feasible to conduct a multi-center blinded trial comparing the delivery of protein at international guideline recommended levels to doses similar to usual care during critical illness.

Keywords:

Enteral feeding, protein, critical illness, nutrition

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Introduction

Many critically ill adults die, with a proportion of survivors experiencing significant muscle wasting and long-term functional impairments[1,2]. During the acute phase of critical illness

delivery of calories via the enteral route has not been shown in any large randomized trial to improve any measured outcome of importance to patients and/or communities[3-7]. Intuitively, increased enteral protein has the potential to reduce muscle wasting and may reduce morbidity and mortality[8,9].

International guidelines recommend delivering protein doses between 1.2-2.0 g/kg/day[10,11], yet observational studies show patients receive considerably less than this[12-16]. Guidelines are based on several observational studies which report higher protein delivery is associated with reduced mortality[14,15,17-20], shorter time to discharge alive[14,17], and reduced duration of mechanical ventilation and intensive care unit (ICU) and hospital length of stay[16]. In contrast, there are observational data reporting inferior outcomes with greater protein doses[21]. Moreover, there are sparse data from randomized trials to confirm either the safety or benefit of increased protein dose in critically ill patients.

Achieving protein doses recommended in international guidelines can be challenging. Strategies such as intravenous amino acids or modular protein doses are available but may require additional lines or place increased burden on staff. To inform a larger trial, we undertook this feasibility trial using a higher protein enteral formula. We hypothesized that delivery of different enteral formulae (high protein or protein doses similar to usual care) would result in: (i) different amounts of protein delivered per group; (ii) one group having protein administration similar to usual care (i.e. ≤1.0 g protein/kg/day) and the other receiving protein doses within international recommendations (~1.2-2.0 g/kg/day); and (iii) clinicians and investigators remaining blinded to the treatment allocation.

Methods

We conducted a randomized, blinded, parallel-group, feasibility trial in six adult ICUs in Australia and New Zealand. The trial was registered prospectively on the Australian and New Zealand Clinical Trials Registry (Approved 02.11.2018; ACTRN12618001829202) and endorsed by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group.

The protocol was approved by the Central Adelaide Local Health Network Human Research Ethics Committee for Australian sites and the Southern Health and Disability Ethics Committee for the New Zealand site. We conducted the trial using a hybrid model of consent: (i) enrolment using a waiver of consent with a notification to the patient or their medical treatment decision maker that they could opt-out of the trial; and (ii) enrolment using a treating clinician 'best interest statement' with relative/Whanau/friend consultation where possible, with permission for continued participation obtained from the patient or their medical treatment decision maker. When patients or their medical treatment decision maker opted out or refused consent to continue participation, we requested permission to retain the data.

Patient population

Eligible patients were: aged ≥18 years; admitted to ICU; undergoing invasive mechanical ventilation; and about to commence or had commenced EN within the preceding 12 hours and were expected to be receiving EN in ICU until at least the calendar day after randomization. Patients were excluded if: they were expected to be receiving oral nutrition before the calendar day after randomization; they had received any EN or parenteral

nutrition (PN) for >12 hours in the current ICU admission; the treating clinician considered the trial EN or rate of delivery to be clinically contraindicated; they had been previously enrolled in the trial; death was deemed imminent or inevitable during the admission; or survival to day 90 was considered unlikely.

Randomization

Using permuted block randomization with variable block sizes and stratified by site, eligible patients were randomized to receive a formula with a greater protein content, designed to achieve protein doses recommended in international guidelines (**high protein group**), or a formula with protein content similar to standard care (**usual care group**) in a 1:1 ratio. Allocation concealment was maintained with a secure, web-based central randomization platform. Study personnel not involved in trial conduct blinded the products, and the randomization schedule was confirmed by an independent statistician not involved in data analysis. Blinded research staff at each site enrolled participants.

Trial EN

Both the high protein (Nutrison Protein Intense; 100g protein/1000ml) and usual care (Nutrison Protein Plus; 63g protein/1000ml) trial formulae were produced and packaged by Nutricia Research B.V. in boxes of 12 OpTri 500ml bottles. Calorie and fat contents, and osmolality of trial formulae were similar, and both were fibre-free. The difference in protein content was balanced by a difference in carbohydrate content (104 compared to 142g /1000ml). Protein sources were similar between the two trial EN formulae, derived from whey, casein, pea, and soy protein. Full product information is available in **Supplemental Table S1**.

Trial EN boxes were labelled with an individual five-digit box number and bottles with the box number and a sequential number from 1 to 12 (**Supplemental Figure S1**). An employee of Nutricia who had no involvement in the trial checked the box numbers against the allocation list prior to the trial EN leaving the Netherlands. A biostatistician at the University of Adelaide, who had no involvement in clinical decision-making and did not participate in the analysis of data (KL) confirmed the randomization schedule and box and pallet labelling against the randomization schedule. Pallets were shipped to Sydney, Australia and then distributed to each of the six ICUs, with logistics co-ordinated within the web-based database. Following randomization, study personnel received notification from the database as to which number box was assigned.

Study procedures

Administration of the trial EN was commenced as soon as possible after randomization. The goal rate for administration for both groups was 1 mL/ kg ideal body weight (IBW)/hour, delivered over 24 hours/day, with IBW (kg) calculated from height measured with the patient lying in bed using a tape measure as previously described[5,22]. The maximum goal rate was set at 100mL/hour, to reduce the risk of potential overfeeding. It was recommended that goal rate was achieved within 48 hours of the commencement of the trial EN[10,23]. Blood glucose concentrations of 180mg/dL (10mmol/L) or less were recommended. All other aspects of nutrition management were handled according to individual unit practice, including rate at which trial EN was commenced and incremented, and strategies to increase nutrient delivery (e.g. prokinetic drugs, post-pyloric tubes). The trial EN was continued until day 28 or until one of the following occurred: (i) cessation of EN by the treating clinician; (ii) the participant was discharged from the ICU; (iii) the treating clinician believed it was in the patient's best interest to cease the trial intervention; (iv) oral nutrition or additional enteral supplements were commenced; or (v) the participant died. Patients discharged and readmitted to the ICU

within 28 days of trial enrolment and still requiring EN were recommenced as per the previous treatment allocation. If the treating clinician deemed supplemental PN necessary, the trial EN was continued unless contraindicated.

Data collection

Baseline data included participant demographics, ICU admission diagnosis and presence of severe head injury (Glasgow Coma Score <8), Clinical Frailty Scale, clinician calculated calorie and protein targets, biochemistry and organ support.

Daily data collected for up to 28 days after randomization included feasibility, biochemical and nutritional outcomes.

Outcomes

The primary outcome was mean daily protein delivery (g/kg IBW/day).

Secondary feasibility outcomes included the recruitment rate, number of feeding days, blinding of intervention, and tolerability of intervention. The adequacy of blinding was evaluated on days 2 and 7, with responses from bedside nurse, treating dietician, and/or treating physician indicating the treatment allocation they thought the patient was receiving. Appropriate labelling of trial EN was also evaluated with an independent analysis of phenylalanine content of blinded trial EN from 28 unallocated boxes (approximately 10% of that allocated to trial patients) using Ultra-Performance Liquid Chromatography-Ultraviolet (UPLC-UV). Tolerability of EN was evaluated daily as episodes of vomiting, need to stop EN for enteral feed intolerance, incident pro-motility drug administration, and bowel dysfunction -

recorded as diarrhoea, defined as the presence of ≥3 loose bowel motions in one calendar day, or rectal tube insertion, or largest gastric residual volume.

Secondary nutritional outcomes included the volume of trial EN and non-trial nutrition and calories delivered. Non-trial protein included protein from non-trial EN, supplemental PN, intravenous amino acids, and enteral protein supplementation. Non-trial calories included non-trial EN and supplemental PN, but not propofol, dextrose, or citrate.

Secondary biochemical outcomes included urea, creatinine, albumin, phosphate, blood glucose, potassium and magnesium (**Supplemental Materials**).

Clinical outcomes collected included mortality (ICU, day 28, and day 90), ventilator- and ICU-free days as defined using published criteria[24] and need for and duration of acute renal replacement therapy. At day 90 participants' residency and health-related quality of life (EuroQol-5D-5L questionnaire) was completed via telephone. The EQ-5D-5L comprises 5 domains ranked as a level of difficulty in completion from 'no problems' (score of 1) to extreme problems (score of 5), as well as a rank of overall health from 'best' (score of 100) to 'worst' (score of 0). The EQ-5D-5L was converted into a single index value after adjustment for country specific value sets. Because there are no country-specific value sets for Australia or New Zealand EQ-5D-5L single index values were calculated using value sets for the United Kingdom and Canada[6,25].

Unless otherwise specified, outcomes were reported for the modified intention to treat population, which were all patients enrolled excluding those who refused participation and refused retention of any data.

Sample size

The initial enrolment number was set at n=120 to allow for separation of the treatment groups for the primary outcome, as well as to establish feasibility. Assuming equal group allocation and an α-level of 0.05, there would be >95% power for group separation, based upon the use of enteral formula suitable for blinding and assuming feed rates equivalent to the TARGET feasibility study[22], with estimated usual care group mean (standard deviation (SD)) of 0.92 (0.32) g protein/kg/day and intervention arm of 1.46 (0.5) g protein/kg/day.

Statistical analyses

Trial data were downloaded as comma-separated text files from the trial database and imported directly into Stata MP/16.1 (Statcorp LLC) for all analyses. Categorical data are presented as number (%), and continuous data as mean (SD) or median [interquartile range, IQR]. Between-group comparisons are reported as the difference in proportions (risk difference) with 95% confidence interval (95% CI), the difference between means (95% CI), or by chi-squared test.

EN delivery (as mL, grams protein, or kcal) is reported as the average total delivered per study calendar day on study days in ICU where trial EN was prescribed. Day 1 and final day of trial EN may be partial days. Group separation was also analysed via plots of the mean daily total values (95% CI) over study days; with population-averaged between-group

estimates generated via generalized estimating equation regression to allow for repeated measures within patients. Data are also presented as per unit time of EN prescription. The percent of the trial EN goal rate that was delivered per hour of EN prescription was calculated as the total volume of trial EN delivered divided by the individual number of hours of trial EN prescribed multiplied by target rate (i.e. only for hours in which EN was prescribed).

Mortality was analysed both as the difference in proportions (95% CI) and as time-to-event analysis, plotted as the treatment group Kaplan-Meier curves censored at day 90, with between group difference assessed via log-rank test.

No imputation was undertaken for missing data, with adjusted denominator numbers included where indicated. P-values were not routinely included given the feasibility design of the trial.

Results

Study population

One hundred and twenty patients were enrolled from 11 April to 3 July 2019, with 90-day follow-up completed on 31 October 2019. Four patients refused ongoing participation and use of data. Of the 116 participants in the modified intention to treat cohort, 58 were assigned to each group. Day 90 mortality was available for 111 patients and functional outcome assessment was completed for 72 participants (**Figure 1**).

Baseline characteristics were similar between the two groups, with both groups having a mean body mass index (BMI) in the overweight category (**Table 1**). Calorie and protein requirements were estimated by a dietician for 48/58 (83%) patients in the high protein arm and 47/58 (81%) patients in the usual care arm (Table 1).

Protein delivery

The use of high protein EN delivered more protein than the usual care arm (1.52 (0.52) vs. 0.99 (0.27) g/kg IBW/day; group difference 0.53 (95% CI 0.38 to 0.69) g/kg IBW/day; $p < 0.001$) (**Figure 2A**). The separation between groups remained whether protein was reported as total grams per day or per kilogram ABW, and whether or not total protein dose included non-trial EN protein sources (**Supplemental Table S2**).

Feasibility outcomes

During the study period the recruitment rate was 0.35 (0.13) patients per day, ranging from 0.19 to 0.50 per day across sites. Time to commence EN following randomization and the duration of trial EN delivery were similar between groups (**Table 2**). Blinding of trial EN was confirmed, with bedside clinicians correctly identifying the high protein formulae in 44% of cases and the usual care formulae in 51% of cases (**Supplemental Table S3**). The analysis of phenylalanine content of trial EN confirmed the blinding of the formulae (**Supplemental Figure S2**). There were no differences in signs, symptoms or treatment of gastrointestinal intolerance between the groups (**Supplemental Table S4**).

Nutritional outcomes

Patients received similar volumes from trial EN (**Table 2**). EN was withheld for similar durations in both groups with no differences in calories delivered (Table 3 and **Figure 2B**).

Biochemical outcomes

The mean daily serum urea was greater in those receiving high protein 14 (7) vs. usual care 11 (5) mmol/L; group difference 3 (95% CI 1 to 5) mmol/L (**Supplemental Figure S3**). There were no differences in any other biochemistry data or insulin administration (**Supplemental Table S5**).

Clinical outcomes

The 90-day mortality rate was 26% with high protein and 27% with usual care, with no between group differences (**Table 3**). Time to death is presented in **Supplemental Figure S4**. Duration of ICU and hospital admission was similar between groups, as were days of organ support (Table 3). Using survivor-only analysis, 61/82 (74.4%) were at home 90-days after randomization with similar residence status at this timepoint (Table 3). The EQ-5D-5L Visual Analogue Score was also similar between groups (Table 3).

Adverse events

There was one reported serious adverse event, which occurred in a patient who had received high protein EN. The patient developed mesenteric ischemia >12 hours after the trial EN had been ceased for tracheal extubation, and they subsequently died. Due to a lack of temporal relationship, this was not deemed to be related to the trial EN. There were two reported adverse events, both relating to elevated urea, with both reported in patients receiving the usual care formulae.

Discussion

We established the feasibility of a multi-center bi-national investigator-initiated blinded randomized clinical trial comparing delivery of formula to provide high protein and protein similar to usual care. Our approach resulted in a group receiving protein doses recommended within international guidelines and a group receiving protein doses similar to usual practice. We established that our screening and randomization processes and blinding of the trial EN were appropriate to minimise bias. Our hybrid consent model and eligibility criteria enabled appropriate recruitment rates and identified a sick cohort of critically ill patients that were exposed to the trial EN for a median of 8 days. We achieved a comprehensive assessment of protein delivery and established separation in protein doses over the entire study duration that included additional protein from other sources.

Our results are similar to observational data that assessed the feasibility of higher enteral protein formulae[26], as well as a previously published smaller randomized trial which found separation in enteral protein dose was achievable whilst maintaining blinding[27]. We now provide evidence that treatment separation is possible in a heterogeneous population of ICU patients over a prolonged period during rapid recruitment. We also recorded protein intake from all sources allowing a comprehensive assessment of protein delivery, with the intervention ceasing only once oral nutrition was commenced. A further strength of our trial is that it was investigator-led, supported by independent funding, and sponsored by a university affiliated hospital, with industry providing trial formula and transport without input into study design or conduct.

The high protein trial EN was associated with a modest but statistically significant increase in daily serum urea concentrations. Similar, albeit larger, differences have been reported in previous trials of increased protein delivery[27,28]. It is important to note that these higher urea concentrations were not associated with increased use of renal replacement therapies. The lack of marked differences in clinical and biochemistry features supports the concept that blinding was maintained.

Point estimates for patient-centered outcomes including mortality were similar between groups. This is consistent with previous meta-analyses of protein administration to the critically ill that reported only modest point estimate effects with wide 95% CI of protein administration on mortality[29,30]. Whilst single-center open-label trials of augmented protein doses suggested by international guidelines suggest that this approach does attenuate muscle wasting[8,31], we observed no signal of beneficial effect on 'downstream' patient-centered outcomes such as health related quality of life. However, attenuation of muscle wasting may not equate to improved quality of life at a later timeframe. These findings should be considered to guide future trial design including sample size calculations and endpoint selection.

Our trial has a number of limitations. We used IBW based on height to guide enteral formulae delivery rather than individual protein dosing according to dietitian recommendations. Although this can be considered a pragmatic approach for prescribing nutritional target rates in the setting of a clinical trial, this approach is less nuanced than expert assessment of an individual prescription. Moreover, when using weight-based dosing there is uncertainty as to whether protein targets should be calculated using ideal, adjusted or actual body weight[10,11]. On any given day an individual patient may not have received protein at doses recommended within clinical practice guidelines but the intention was that

the mean delivery was within these guidelines. It should be recognized that our 'usual care' arm may not contain protein doses representative of standard care at all centers; however, recent updates of international guidelines to recommend higher protein doses is likely to mean current standard practice provides greater protein delivery than historical data suggests. We ceased the intervention when patients commenced oral intake or were discharged from ICU and the impact of post-ICU nutrition is currently unknown[32] There was a greater loss to follow-up than anticipated in this trial for secondary outcomes; however, given the feasibility design, the trial was not powered to show differences in clinical outcomes. Loss to follow-up in survivors may not be a random phenomenon and may increase the risk of incorrect conclusions regarding clinical outcomes. Finally, we did not measure nitrogen balance, which may be considered a surrogate measure for protein breakdown[33].

Conclusions

We conducted a multi-center parallel group blinded randomized clinical trial with one group receiving protein doses via the enteral route that are recommended within international guidelines and the other group receiving protein doses similar to standard practice. Our trial was able to rapidly recruit patients who received the trial EN for a median of 8 days with clinicians blinded throughout and found no signal of harm from high protein EN.

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Table 1: Baseline characteristics of the trial patients

Variable	**High Protein (n=58)**	**Usual Care (n=58)**
Age (years), median [IQR]	60 [50, 72]	61 [46, 68]
Sex (male), n (%)	39 (67)	44 (76)
APACHE II score, median [IQR]	22 [16, 26]	22 [16, 27]
ICU admission category, n (%)		
Non-operative	47 (81)	41 (71)
Elective surgery	2 (4)	8 (14)
Emergency surgery	9 (16)	9 (16)
Body Mass Index (kg/m^2) from actual body weight	29 [26, 33]	30 [25, 34]
Actual Body Weight (kg)[1]	85 [75, 100]	85 [75, 101]
Ideal Body Weight (kg)[2]	65 [57, 71]	67 [57, 72]
Clinical Frailty Score at randomization		
Very fit	3 (5)	6 (10)
Well	14 (24)	10 (17)
Managing well	13 (22)	20 (34)
Vulnerable	11 (19)	9 (16)
Mildly frail	5 (9)	3 (5)
Moderately frail	5 (9)	4 (7)
Severely frail	5 (9)	3 (5)
Unknown	2 (3)	3 (5)
Organ support at randomization, n (%)		
Vasopressor	37 (64)	37 (64)
Renal replacement therapy	4 (7)	2 (3)
Energy requirements as per clinician (n=95)[3]		
Kcal/day, median [IQR]	1882 [1503, 2050]	1900 [1628, 2075]

Kcal/kg IBW/day, median [IQR]	29.0 [26.2, 31.8]	29.1 [27.2, 30.8]
Protein requirements as per clinician (n=95)[3]		
Gram/day, median [IQR]	95 [79, 104]	95 [85, 108]
Gram/kg IBW/day, median [IQR]	1.46 [1.31, 1.58]	1.47 [1.38, 1.57]
Time from ICU admission to randomization (hrs), median [IQR]	17 [8, 29]	16 [10, 24]
Pre-randomisation urea (mmol/L), median [IQR]	9 [6, 13]	9 [5, 11]
Pre-randomisation creatinine (μmol/L), median [IQR]	111 [82, 179]	124 [81, 241]
Pre-randomisation albumin (g/L), median [IQR]	27 [24, 30]	28 [22, 32]

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit; IQR: Interquartile Range

[1]Actual body weight was estimated or measured and was not used to determine trial enteral nutrition target rate

[2]Ideal body weight calculated from: men = (height (cm) – 152.4) * 0.9 + 50 and women = (height (cm) – 152.4) * 0.9 + 45.5

[3]Note clinician estimated energy and protein requirements were available for 95 patients only

Table 2: Feasibility outcomes

Variable	**High Protein (n=58)**	**Usual Care (n= 58)**	**Difference (95%CI)**
Hours from randomization to first trial EN commencement, mean (SD)	2 (5.6)	1.6 (1.5)	0.4 (-1.1, 1.9)
Duration of trial nutrition, days, mean (SD)	8.7 (7.3)	8.1 (6.3)	0.5 (-2, 3)
Trial EN: mean (SD)			
Volume – mL/day	979 (387)	1008 (315)	-29 (-159, 101)
Calories delivered – kcal/kg IBW/day	19.2 (6.5)	19.6 (5.4)	-0.4 (-2.6, 1.8)
EN Hold[1] (≥2 hrs - % days), median [IQR]	15 [0, 31]	15 [0, 27]	P>0.99

EN: Enteral Nutrition; IBW: Ideal Body Weight; IQR: Interquartile Range; SD: Standard Deviation

[1]EN hold includes any documented period for which trial EN was held for ≥2 hours.

Table 3: Clinical outcomes

Variable	**High Protein (n=58)**	**Usual Care (n= 58)**	**Difference (95%CI)**
Mortality, n/N (%)			
ICU	12/58 (21)	10/58 (17)	3.4 (-10.8, 17.7)
28-day	12/56 (21)	14/57 (25)	-3.1 (-18.6, 12.4)
90-day	14/55 (26)	15/56 (27)	-1.3 (-17.7, 15)
Length of stay (days), mean (SD)			
ICU	13 (13)	14 (18)	-1 (-6.8, 4.9)
Hospital	24 (21)	26 (32)	-1.5 (-11.4, 8.4)
Days alive and ICU free at day 28, mean (SD)	17 (7.5)	17 (7.7)	0.1 (-2.7, 2.9)
Days alive and IMV free at day 28, mean (SD)	18 (9)	18 (9)	-0.4 (-3.7, 2.9)
Vasopressor support			
Received vasopressors, n (%)	48 (83)	51 (88)	-5.2 (-18, 7.7)
Proportion of study days, % mean (SD)[1]	54 (30)	47 (22)	7.4 (-3, 17.8)
Renal replacement therapy			
Received renal replacement therapy, n (%)	12 (21)	13 (22)	-1.7 (-16.7, 13.2)
Proportion of study days, % mean (SD)[1]	57 (27)	49 (24)	8.5 (-12.5, 29.4)
Destination at hospital discharge, n (%)	*n = 44*	*n = 44*	
Home	18 (41)	23 (52)	
Rehabilitation facility	17 (39)	13 (30)	p = 0.68
Another acute care hospital	8 (18)	7 (16)	
Chronic care facility	-	1 (2.3)	
Other	1 (2.3)	-	

Residence at day-90 post-randomization, n (%)	*n = 41*	*n = 41*	
Home	31 (76)	30 (73)	
Rehabilitation facility	5 (12)	6 (15)	
Another acute care hospital	1 (2.4)	-	p = 0.85
Chronic care facility	2 (4.9)	1 (2.4)	
Still in hospital	1 (2.4)	1 (2.4)	
Still in ICU	-	2 (4.9)	
Other	-	1 (2.4)	
Unknown	1 (2.4)	-	
EQ-5D-5L (Domains) at day 90, mean (SD)			
Mobility	2.2 (1.3)	2 (1.3)	0.2 (-0.4, 0.8)
Self-care	2 (1.2)	1.7 (1.3)	0.3 (-0.3, 0.8)
Usual activities	2.5 (1.3)	2.1 (1.3)	0.4 (-0.2, 1)
Pain or discomfort	1.8 (0.9)	1.9 (0.9)	-0.1 (-0.5, 0.4)
Anxiety / depression	1.8 (0.9)	1.8 (0.9)	0 (-0.4, 0.4)
EQ-5D-5L VAS at day 90, mean (SD)	60 (32)	53 (32)	7 (-6.7, 20.6)
EQ-5D-5L (Standardized valuation weights)			
United Kingdom population weights	0.7 (0.28)	0.76 (0.23)	-0.06 (-0.18, 0.06)
Canadian population weights	0.71 (0.25)	0.76 (0.21)	-0.05 (-0.16, 0.06)

EQ-5D-5L VAS: EuroQol-5D-5L Visual Analogue Scale; IMV: Invasive mechanical ventilation; ICU: Intensive Care Unit; SD: Standard deviation

[1]Proportion of study days in which therapy received is calculated only in those receiving. Study days included days on which trial EN was prescribed from initiation to cessation, excluding days on which no trial EN was delivered.

Figure 1: CONSORT diagram/ patient flow diagram

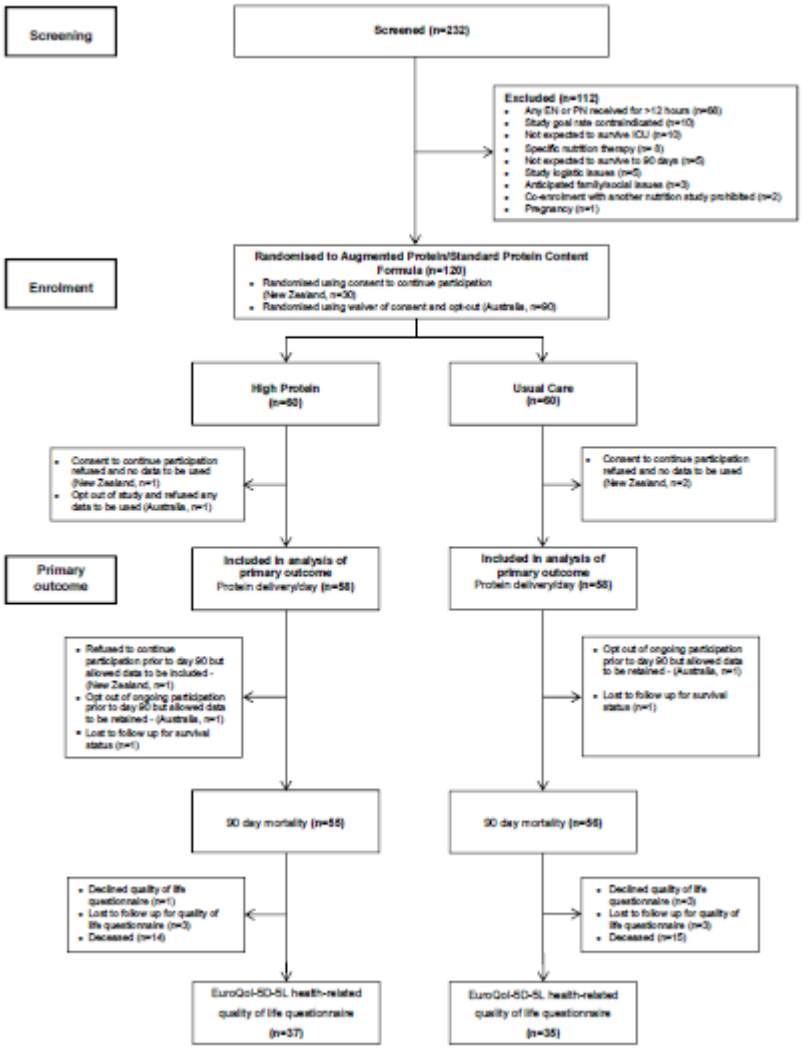

Figure 2: Study group (solid squares = High Protein / open circles = Usual Care) over study day plots for mean and half-95% CI for (A) protein dose in grams per kilogram of ideal body weight per day, and (B) energy delivery, in kcal per day. Total trial group numbers remaining are included above the x-axis. As trial enteral nutrition delivery was isocaloric, the plot for volume (mL/day) is effectively identical to (B) and not shown.