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# Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial)

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### **Conflicts of interests**

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### **Abstract**

**Background:** International guidelines recommend greater protein delivery to critically ill patients than they currently receive. This pilot randomized clinical trial aimed to determine whether a volume-target enteral protocol with supplemental protein delivered greater amounts of protein and energy to critically ill patients compared to standard care.

**Methods:** Sixty participants received either the intervention (volume-based protocol, with protein supplementation) or standard nutrition care (hourly rate based protocol, without protein supplementation) in the intensive care unit (ICU). Co-primary outcomes were average daily protein and energy delivery. Secondary outcomes included change in

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quadriceps muscle layer thickness (QMLT, ultrasound) and malnutrition (Subjective Global Assessment) at ICU discharge.

**Results:** Mean (SD) protein and energy delivery per day from nutrition therapy for the intervention were 1.2 (0.30) g/kg and 21 (5.2) kcal/kg compared to 0.75 (0.11) g/kg and 18 (2.7) kcal/kg for standard care. The mean difference between groups in protein and energy delivery per day was 0.45 g/kg (95%CI 0.33 – 0.56,  $p < 0.001$ ) and 2.8 kcal/kg (95%CI 0.67 – 4.9,  $p = 0.01$ ). Muscle loss (QMLT) at discharge was attenuated by 0.22 cm (95%CI 0.06 – 0.38,  $p = 0.01$ ) in patients receiving the intervention compared to standard care. The number of malnourished patients was fewer in the intervention (2 (7%) vs. 8 (28%),  $p = 0.04$ ). Mortality and duration of admission were similar between groups.

**Conclusion:** A high protein volume-based protocol with protein supplementation delivered greater amounts of protein and energy. This intervention was associated with attenuation of QMLT loss and reduced prevalence of malnutrition at ICU discharge.

**Trial registration:** This trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.ANZCTR.org.au/> ACTRN:12615000876594, UTM: U1111-1172-8563.

**Key words:** Critical illness, dietary proteins, enteral nutrition, enteral formulas, nutritional support, ultrasound, muscle mass and functional outcomes.

**Clinically relevant statement:**

Current international guidelines recommend that critically ill patients should receive at least 1.2-2.0 g/kg per day of protein. In clinical practice patients often receive considerably less protein due, in part, to healthcare factors (interruption to nutrition therapy for other medical therapy) and patient factors (feeding intolerance). The aim of this pilot randomized clinical

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trial was to determine whether an high protein enteral feeding protocol using a volume target and protein supplementation delivered greater amounts of protein and energy to critically ill patients when compared to standard care. In this single center, open label, parallel group trial of critically ill mechanically ventilated patients the intervention was associated with greater delivery of protein and energy, attenuation of muscle loss and a lower prevalence of malnutrition at ICU discharge. Further research using this intervention is warranted given the achievement of recommended protein delivery and observed point estimates favouring beneficial effect in key secondary outcomes.

## **Introduction**

The current Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition guidelines recommend that protein should be provided at a level of 1.2-2.0 g/kg/day, with possibly greater amounts for patients who are obese or present with multi-trauma or burns (1) and other guidelines have similar recommendations (ref ESPEN). However, there is a lack of high-quality randomized controlled trials to support these protein recommendations (2, 3).

Observational data suggest that greater protein provision may be associated with improvements in survival, ventilator free days and time to discharge alive from the Intensive Care Unit (ICU) (4-8). Higher levels of protein provision may not only reduce mortality but also stimulate the synthesis of new proteins and preserve muscle mass (3). Skeletal muscle preservation has been identified as an important surrogate outcome of ICU patients given of the association between muscle loss and the development of ICU-acquired weakness (9, 10). Optimal nutrition, particularly with adequate protein provision may have the capacity to attenuate muscle loss (11, 12) but randomized controlled trial data to substantiate this are limited (13).

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Despite current guidelines, the delivery of nutrition in the ICU is substantially less than recommended (14). The provision of nutrition via the enteral route is considered preferable (1), however adequate delivery of protein and energy to critically ill patients via this route remains a challenge (15). Standard enteral feeding regimens are based on energy targets and as a result protein delivery is more often restricted by the formula composition; this may result in protein prescriptions that are less than the current guidelines (3). Several methods to increase protein delivery via the enteral route have been proposed, these include the use of high protein formulas, volume based feeding protocols and additional protein supplementation (16). However in practice, these methods may not result in more protein and energy being administered as protein is a potent stimulant of the small intestine feedback loop which slows gastric emptying (17) and can cause feed-intolerance (18) thereby possibly reducing protein and energy provision. The combination of these methods has not previously been studied.

The primary aim of this single center pilot randomized controlled trial was to determine whether a high protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly rate based nutrition protocol without protein supplementation to mechanically ventilated critically ill patients. The secondary aims were to evaluate if this intervention increased feed-intolerance or the development of diarrhea, whether the intervention attenuated muscle or weight loss or the prevalence of malnutrition at ICU discharge, and to estimate the impact of the intervention on patient-centered outcomes.

## **Materials and methods:**

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The study protocol was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.ANZCTR.org.au/> Registration number UTN: U1111-1172-8563). A protocol and statistical analysis plan manuscript was submitted during the enrolment period, prior to analysis of data (19).

## **Patients**

This trial was conducted between August 2015 and August 2017 at the Royal Melbourne Hospital ICU. This ICU is a 32-bed University affiliated, tertiary referral, mixed medical-surgical-trauma ICU. Screening was only performed on weekdays. Patients were eligible if they were greater than 18 years of age, mechanically ventilated for < 48 hours, and were anticipated to remain ventilated for at least 72 hours. Patients were excluded if they had a contraindication to enteral feeding, if there was futility of care or death was imminent, if they had a pre-morbid disability resulting in an inability to ambulate greater than 10 meters, if they were pregnant or the treating clinician considered the intervention was not in the patient's best interest. The trial was conducted in accordance with the declaration of Helsinki and prior informed consent was obtained from the surrogate decision maker. Continuation of participation was obtained if the participant recovered adequately to provide consent. The protocol and consent process was approved by the Royal Melbourne Hospital Human Research Ethics Committee (2015.048).

The overall sample size of 60 patients (two groups of 30 patients) was calculated using a two-sided  $\alpha$  level of 0.05 and a power (1- $\beta$ ) of 80% to detect a minimum difference of 15 g protein delivered per day between groups based on data from an observational study undertaken within the trial ICU (20), which showed a baseline protein intake [mean (SD)] of 50.8 (20.1) g/day. Using data from the VALIDUM study (21), mean (SD) quadriceps muscle layer thickness (QMLT) was 1.3 (0.6) cm (21), suggesting that a sample size of 27

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participants in each group, accounting for 10 percent missing data, was sufficient to also provide more than 80% power to detect a mean difference of 0.5 cm in QMLT between groups.

### **Study design**

Participants were randomly assigned using a simple 1:1 randomization system to receive either the intervention or standard care. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes that were held in a secure location by research personnel not involved with the trial. Due to the nature of the intervention clinicians were not blinded; however blinded assessors undertook the outcome measurements of muscle strength and physical function.

The intervention or standard care was delivered following randomization until ICU discharge; or until the patient no longer required enteral tube feeding, or the end of study day 15, whichever came first. Feeding intolerance was managed for both groups according to standard unit protocols, which included the use of gastrokinetic drugs, without ceasing enteral nutrition, and the consideration of post pyloric feeding tubes or supplemental parenteral nutrition if severe feeding intolerance occurred. The need for parenteral nutrition was determined by treating physicians who were not study investigators. The intervention group receive a volume based nutrition protocol (16) using a high protein enteral formula (Nutrison® Protein Plus, Nutricia, Zoetermeer, The Netherlands; 63g protein and 1250 kcal per liter). Nursing staff were provided with a detailed regimen, which included a volume target and an hourly rate target with instructions to deliver the volume target over a 24 hour period based on 25 kcal/kg/day. Nursing staff assessed the volume of feed that had been delivered at 16:00 each day and calculated the volume required for the remaining 8 hours in order to achieve goal volume and adjusted the rate accordingly. A maximum rate of 150 ml/hr was set to minimize the risk of aspiration (16). Protein supplements (Beneprotein®,

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Nestle Health Sciences, Switzerland, 6g of protein per scoop) were prescribed by the study dietitian in an attempt to achieve delivery of 1.5 g/kg/day protein (liquid formula plus protein supplement). The standard care group received standard nutrition care (22), which included commencing a standard commercially available 1.0 kcal/ml enteral formula (Nutrison® 1.0kcal, Nutricia, Wuxi, China), which provides 40 g protein and 1000 kcal per liter. Enteral nutrition was commenced as per the standard facility protocol, aiming to provide 1.0 g/kg/day protein and 25 kcal/day (1). For both groups the weight used to calculate the nutrition provision was based on actual body weight or ideal body weight if above the healthy weight range. Weight was obtained using the bed scales and height was calculated using the estimate provided by measuring ulna length (23). Ideal body weight for participants aged < 65 years is defined as a Body Mass Index (BMI) between 18.5 and 25kg/m<sup>2</sup> and for those aged ≥ 65 years, a BMI between 22 and 27kg/m<sup>2</sup> (24). For participants with a BMI ≥ 32kg/m<sup>2</sup> an adjusted ideal body weight was used (ideal body weight + 25% (actual body weight – ideal body weight) (25).

At baseline, data was collected including admission diagnosis, Charlson Comorbidity Index, Katz Activities of Daily Living (ADL) index, Acute Physiology and Chronic Health Evaluation II and III (APACHE II and III) score, and admission Sequential Organ Failure Assessment (SOFA) Score. Duration of ICU and hospital admission, discharge destination and survival at days 28 and 60 were recorded.

### **Protein and energy provision**

The co-primary outcomes were the mean daily protein and energy delivered over the 15 day study period. Administration of nutrition prior to commencing the study protocol was not included. The provision of protein and energy was calculated on a daily basis from enteral and/or parenteral formula and/or protein supplements but separate from all other sources.

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Total energy delivery included nutrition therapy as well as calories from dextrose and propofol. Day 1 (day of randomization) and day of discharge were included even if they were partial days.

### **Feeding intolerance**

The proportion of patients who developed feeding intolerance was determined by the number of patients in the group who had at least one gastric residual volume > 300 ml (18) over the study period. The cumulative incidence of feeding intolerance was determined by the number of days a patient had gastric residual volumes > 300 ml. The proportion of patients who developed diarrhea was determined by the number of patients who had more than 3 bowel actions or greater than 300 ml of stool output in a 24 hour period on at least one occasion (26) and the cumulative incidence was determined by the number of days the patient met the above criteria.

### **Muscle mass**

Muscle mass was assessed with ultrasound, measuring QMLT using the technique described by Tillquist and colleagues (27). The QMLT measurements were performed by a single trained operator (KF) using a portable ultrasound machine (Sonosite S-ICU™) with a multiple frequency transducer (13-6MHz, 6cm). The device settings were standardized and the measurements were taken with the patient lying in a supine position with legs relaxed and extended. QMLT was completed on bilateral lower limbs; measurements were obtained at two different landmarks; the midpoint and two thirds between the Anterior Superior Iliac Spine and the upper pole of the patella (21, 27, 28). A still image was taken with the transducer held perpendicular to the skin; the muscle thickness was quantified by using the onscreen callipers to measure the distance between the upper margin of the femoral bone and the lower boundary of the deep fascia of the rectus femoris muscle (21). Duplicate

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measurements were taken at each landmark and the mean of the four linear thicknesses were calculated for each leg separately (28). The first measurement was taken before randomization and then at discharge from ICU or day 15 (whichever came first).

#### **Nutritional assessment and outcomes:**

Prior to randomization baseline measures were undertaken including height (cm) (using ulna length (23)), body weight (kg) (from bed scales), BMI ( $\text{kg/m}^2$ ), mid upper arm circumference (cm), nutritional status using the subjective global assessment (SGA) (29), plasma albumin (g/L) and an estimate of energy and protein requirements obtained by an independent dietician. Body weight, nutritional status, mid upper arm circumference and plasma albumin levels were repeated at discharge from ICU or day 15, whichever came first. Additionally measured energy expenditure (MEE) was assessed by indirect calorimetry using the E-sCOVX (GE, Helsinki, Finland) monitor (30, 31). The measurements were carried out within the first 5 days following enrolment, if a trained operator was available, patients were excluded if they were on continuous renal replacement therapy, attached to extracorporeal circulation, had an intercostal catheter with an air leak or were receiving a fraction of inspired oxygen greater than 0.6 (32). The measurement was completed with the patient in a fed state lying supine. The mean respiratory quotient (RQ) and MEE (kcal/day) were recorded.

#### **Functional outcomes**

Muscle strength was assessed in suitable participants using handgrip dynamometry and the Medical Research Council (MRC) scale (33, 34). The first muscle strength test was performed at awakening (34) and then again at discharge or day 15, whichever came first. Patients were screened for attention and comprehension on the basis of their ability to follow commands, they were considered awake if they scored at least three out of five using the De Jonghe comprehension criteria on at least two occasions within a six hour period and had a

Riker sedation-agitation scale score of three to five. Handgrip dynamometry (Commander Echo™ Wireless Grip Dynamometer, USA) was measured in both limbs with the participant in a chair or sitting at least at 45 degrees in bed, with the patient's elbow at 90 degrees supported by a pillow or the arm of the chair. The Medical Research Council sum score (MRC-SS) was measured as previously described (35) with ICUAW defined as an MRC-SS of < 48/60 (36-38). Physical function was assessed using the physical function in Intensive Care Test-scored (PFIT-s) (39)

### **Statistical analysis**

Statistical analysis was performed using IBM SPSS Statistics (IBM® SPSS® Statistics Premium Grad Pack Version 23.0) and Stata (Stata Statistical Software: Release 15. College Station, TX: StataCorp LP; 2017). All analyses were conducted using the intention-to-treat patient sample. Baseline patient demographics, severity of illness, ICU length of stay, mortality and nutritional markers were tabulated according to treatment group and summarized as mean (standard deviation) (SD) or median and [Interquartile range] [IQR], as appropriate. Initial exploratory data analysis included the calculation of summary statistics, and comparison between treatment groups using non-parametric (Wilcoxon), parametric (t-test) and Fisher exact tests as appropriate, as well as construction of trajectory plots according to treatment group. The co-primary outcomes of average daily energy and protein delivery were compared between the two groups using two-sample unpaired t-tests, with statistical significance for each set conservatively at two-sided values of 0.025, to control the family-wise type 1 error to less than 0.05 overall.

All secondary outcomes were regarded as exploratory and hypothesis-generating with, as a consequence, no adjustment for multiple comparisons to their conventional 5% type 1 error thresholds. Group differences for each patient's discharge QMLT were compared after

adjustment for initial baseline values and other selected covariables using linear regression (analysis of covariance, ANCOVA). Robust standard errors were specified to allow for within subject correlation of the repeated muscle mass observations from left and right sides and across time. No imputation of missing data was performed. Standard model diagnostics of linearity and influence were performed.

## Results

A total of 885 mechanically ventilated patients were screened, with 160 patients found to meet the eligibility criteria (Figure 1). Consent was obtained for 60 patients, who were randomized to receive either the intervention (n = 30) or standard care (n = 30). The goals of medical treatment were changed to 'comfort care' for one patient (intervention group) soon after randomization but prior to commencement of the intervention nutritional regimen. One patient from each group was liberated from the ventilator prior to 48 hours.

Figure 1. Patient flowchart, flow diagram of patient eligibility and study conduct

At baseline, participants in both groups were similar with regards to age, sex, APACHE II and III scores, BMI, admission weight and co morbidity index (see Table 1). The majority of the patients in both groups were classified with medical rather than surgical diagnoses.

Table 1. Baseline demographics and comparisons of study groups

### Co-primary outcomes

The intervention was associated with an increased total protein delivery over the study period [mean increased protein delivery of 37 g/day (95%CI 26 to 47, p <0.001)], equivalent

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to a mean overall protein advantage of 0.45 g/kg/day (95%CI 0.33 to 0.56,  $p < 0.001$ ) (Table 2). A difference was observed over multiple days, with significantly more protein delivered to the intervention group compared to control group on 13 of the 15 study days (Figure 2A and Table 2).

The intervention was also associated with increased energy delivery from enteral nutrition per day [mean increase of 2.8 kcal/kg (95%CI 0.7 to 4.9,  $p = 0.01$ )] (Table 2). There was increased energy delivery from nutrition on 5 of the 15 study days (Figure 2B) and total energy delivered was greater in the intervention group [mean difference of 237 kcal/day (95%CI 10 – 464,  $p = 0.04$ ) (Table 2).

Figure 2. Daily protein (2A) and energy (2B) provision from nutrition and total energy delivery (2C) over the study period

Table 2. Primary outcomes and nutritional provision

### **Nutritional provision and outcomes**

The participants required enteral nutrition following randomization for a mean of 8.0 days (4.4) in the intervention and 7.0 days (4.5) in the standard care group [mean difference 1.0 day (95%CI (-1.3 – 2.3),  $p = 0.87$ )]. Estimated energy and protein requirements were similar between groups (Table 2). Energy expenditure was measured in a convenience sample of 15 patients from each group (50%) and the daily energy expenditure was similar between groups (Table 2). Nutritional adequacy was greater in the intervention group (Table 2). Enteral nutrition was commenced earlier in the intervention group and the period of time fasting was similar between groups (Table 2). Two patients in the standard care group and no patients in the intervention group received parenteral nutrition for a mean of 4.5 days in combination with enteral nutrition due to feeding intolerance. The proportion of patients who

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developed feeding intolerance or diarrhea and the cumulative incidence of these were similar between groups (Table 3). There were fewer patients in the intervention group classified as malnourished (SGA assessment) at ICU discharge but all other assessed nutritional outcomes, including weight loss, were similar between groups (Table 3).

Table 3. Nutrition outcomes

### **Muscle mass outcomes**

QMLT measurements were not available at baseline and discharge in 6 (23%) participants in the intervention group and 7 (27%) participants in the standard care group. These missed observations were primarily due to participant unavailability, a change of focus to comfort care, death, other medical issues or discharge from intensive care when the primary investigator was not available. Adjusted for baseline QMLT, the intervention was associated with less QMLT loss at discharge, with a mean attenuated loss of 0.22 cm (95%CI 0.06 to 0.38,  $p = 0.01$ ), controlling for patient age, severity of illness (APACHE III score), BMI and admission category (Table 4.). Greater baseline QMLT was associated with a greater absolute QMLT at discharge, and surgical patients appeared to lose more QMLT compared to medical patients [-0.28 cm (95% CI -0.44 to -0.01,  $p = 0.01$ )].

Table 4. Effect of the treatment on QMLT at discharge

### **Physical assessment outcomes**

Only 6 (20%) participants in the intervention and 16 (53%) participants in the standard care group completed handgrip strength, 7 (23%) and 14 (47%) participants completed MRC-s muscle strength measurements and 8 (27%) and 14 (47%) participants completed physical function tests respectively. The missed observations were primarily due to participants' inability to complete these assessments based on the de Jonge criteria or participant

unavailability as above. In this small patient subgroup, the intervention and control groups showed similar muscle strength, physical function and clinical outcomes (Table 5).

Table 5. Functional and other secondary outcomes

## Discussion

This trial prospectively randomized participants to receive an enteral feeding intervention that resulted in delivery of considerably more protein and energy delivery via nutrition therapy compared with standard care. Importantly, the intervention did not appear to increase adverse events, such as feed-intolerance or diarrhea and the proportion of patients who developed these issues was consistent with observational literature (15, 40). Moreover, the intervention was associated with attenuation of QMLT loss and a reduced proportion of malnourished patients on discharge from ICU, without other signals of harm in terms of other patient-centered outcomes.

In this trial, the intervention resulted in greater protein and energy delivery, which is consistent with previous studies of volume-based feeding (16, 41). Heyland and colleagues described a novel multi-modal approach termed the “PEP uP protocol”, which incorporated a volume-based enteral feeding regimen (16, 41). In a single center sequential period feasibility study the point estimates of enteral protein and energy delivery were augmented by approximately 10 percent, with nutritional adequacy improving from, mean (SD), 74 (29) percent (41). In a subsequent prospective cluster randomized trial of 18 ICUs, those sites that were allocated to the PEP uP protocol delivered 14 percent more protein and 12 percent more calories than the control sites, however the overall nutritional adequacy with the intervention was, mean (SD) 48 (33) percent (16). Subsequently, a single center randomized control trial utilized a similar PEP uP style protocol and reported that a volume based feeding

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protocol delivered more energy (mean (SD), 93 % (17)) compared to a rate based feeding protocol (81 % (19)) in critically ill patients, however protein delivery was not reported (42). Moreover, none of the previous mentioned trials of volume-based regimens incorporated functional effects of nutrition such as muscle mass or strength measures. This current trial also differs from previous trials in that prophylactic gastrokinetic drugs and semi-elemental formulae were not prescribed. In addition, the strategy to aid adherence to the volume target implemented included requesting staff to assess nutrition delivery at a set time point in the day (1600 h) rather than at the time of the interruption. Lastly, additional protein was supplemented throughout the study period.

While there is considerable enthusiasm for, and face-validity underlying, greater protein delivery to improve patient-centered outcomes (3), there is limited evidence to support this intervention. In a systemic review of all relevant randomized controlled trials (43), increasing protein delivery did not improve patient-centered outcomes, although the authors noted that none of the included studies compared standard protein provision with the current guideline recommendations. Ferrie and colleagues recently reported the impact of delivering different intravenous protein doses (13). In this study of 119 critically ill patients the augmented protein intervention was associated with improvements in surrogate outcomes including handgrip strength, reduced fatigue and greater forearm muscle thickness (13). Collectively, the results of Ferrie (13) and the current trial provide preliminary single-centre trial evidence that early protein delivery within the guideline range may attenuate muscle loss in critically ill patients. This concept is also supported by a number of observational studies (4, 5, 8, 44-46), however conflicting data have been reported. In the multi-center UK MUSCLE study greater loss of quadriceps muscle was associated with more protein delivery (47). Furthermore, in rabbits studied after burn injury administration of amino acids was associated with an increase in muscle vacuolization (48) and in a pediatric population

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increasing doses of intravenous protein were associated with inferior patient-centered outcomes (49). Accordingly, the point estimates in the current trial favoring improvement in surrogate outcomes (QMLT and SGA) should be interpreted with caution.

### **Clinical significance**

The intervention achieved treatment separation between the groups, with the increase in protein delivery to be at least 0.33 g/kg/day and as much as 0.56 g/kg/day. Particularly in those patients admitted and exposed to the intervention for longer periods, it is possible that this magnitude of protein supplementation could limit the muscle mass losses, commonly observed in critical care patients, or otherwise improve patient-centered outcomes.

### **Strengths and limitations**

The strengths of this trial include allocation concealment and randomization to limit selection bias, as well as submission of protocol and planned statistical analysis prior to completion of the trial (19). The study aimed to provide two different protein targets using enteral nutrition. The intervention delivered protein within the current guideline recommendations and the control group received care (protein and energy delivery) representative of routine care in Australia and New Zealand (22).

The limitations of this trial include conduct at a single center without a practical method of blinding the intervention, making further validation in other settings desirable. As a pilot trial with a relatively small cohort the point estimates for important surrogate outcomes, such as QMLT, must be interpreted with considerable caution and may not represent effects at a population level. Also, the intervention was a volume-based protocol with protein supplementation meaning energy delivery was also increased, which may confound the observed impact of protein on outcomes. Missing data for some of the secondary and

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tertiary outcomes, particularly for the functional measurements, makes any estimates of effect provisional (50). Lastly, only mechanically ventilated enterally fed critically ill patients were enrolled and of the participants the majority fell into broad medical or trauma classifications. Accordingly, the present data may not be generalizable to patients requiring parenteral nutrition or those with primary gastrointestinal disease.

## **Conclusion:**

A high protein volume-based enteral feeding protocol with supplemental protein delivered greater amounts of protein and energy to critically ill mechanically ventilated patients. This intervention was associated with attenuation of muscle loss and reduced prevalence of malnutrition at ICU discharge. These data support the feasibility and clinical relevance of further investigations using this intervention.

## **Statement of Authorship**

K. Fetterplace, C. Maclsaac and L. J. Beach and A. Tierney equally contributed to the conception and design of the research; A. M. Deane, M Mourtzakis and A.Forsyth contributed to the design of the research; K. Fetterplace, B. M.T. Gill, T. Rechnitzer, L. Beach and L. D. Knight contributed to the acquisition of the data; K. Fetterplace and J. Presneill contributed to the analysis and the interpretation of the data; and K. Fetterplace and A. M. Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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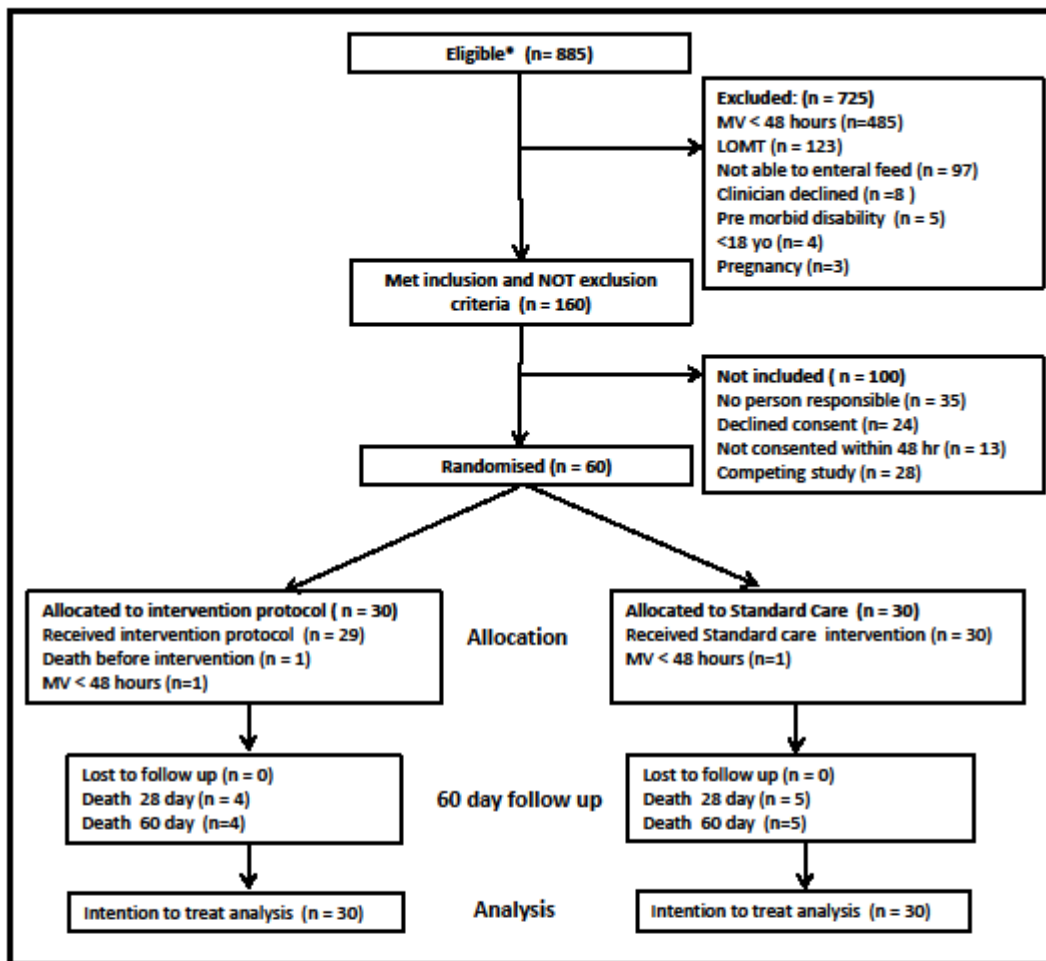
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### Figure 1. Patient flowchart, flow diagram of patient eligibility and study conduct

Abbreviations: LOMT, Limit of medical treatment; n, number of participants; MV, Mechanically ventilated; yo, years old

\*Eligible patients - patients mechanically ventilated and admitted to the ICU <48 hours at time of screening



A



**Table 1.** Demographics and comparisons of study groups<sup>a</sup>

<b>Demographics</b>	<b>Intervention (n= 30)</b>	<b>Standard (n = 30)</b>
Age, years	55 (13)	57 (16)
Sex, Male, n (%)	23 (77)	21 (70)
BMI, kg/m <sup>2</sup>	30 (7.1)	29 (5.3)
APACHE II Score	22 (6.2)	20 (5.9)
APACHE III Score	77 (25)	71 (22)
Comorbidity Index	3 [1 – 5]	3 [2 – 4]
Katz ADLs Index	6 [6 – 6]	6 [6-6]
<b>Admission Category, n (%)</b>		
Medical	21 (70)	16 (53)
Elective Surgery	1 (3.3)	1 (3.3)
Emergency Surgery	8 (27)	13 (43)
<b>Admission Diagnosis, n (%)</b>		
Neurological conditions	13 (43)	7 (23)
Multi-trauma/head-trauma	7 (23)	11 (37)
Respiratory	1 (3.3)	5 (17)
Cardiac arrest	3 (10)	1 (3.3)
Sepsis	3 (10)	1 (3.3)
Cardiac surgery	0	2 (6.7)
Other	3 (10)	3 (10)
Chronic Renal Failure, n (%)	1 (3.3)	0 (0)

**Abbreviations:** ADL, Activities of Daily Living; APACHE - Acute Physiology and Chronic Health Evaluation; BMI, Body mass index; kg, kilograms, m, meters; n, number of participants

<sup>a</sup>Values are represented as mean (SD), median [IQR] or n (%) if list in table

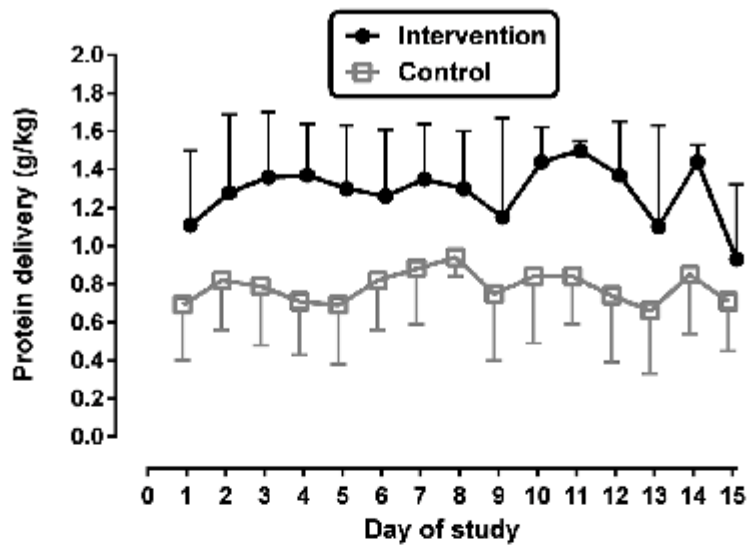
**Figure 2.** Figure 2. Daily protein (2A) and energy (2B) delivery from nutrition and total energy delivery (2C) over the study period

**Abbreviations:** g, grams; kcal, kilocalories; kg, kilograms

Mean daily protein (2A), Energy (2B) and total energy (2C) delivery according to research group, with error bars representing one standard deviation

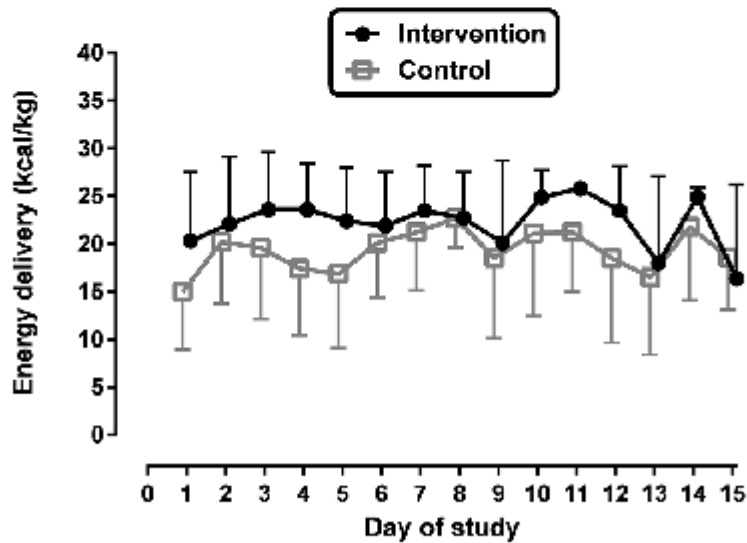
\*Total energy delivery includes energy from nutrition therapy plus calories from dextrose and propofol

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Intervention (n)	30	27	17	15	13	10	8	3
Control (n)	30	27	24	12	9	8	5	4

Figure 2A.



Intervention (n)	30	27	17	15	13	10	8	3
Control (n)	30	27	24	12	9	8	5	4

Figure 2B.

A

**Table 2.** Primary outcomes and nutrition provision<sup>a</sup>

Outcomes	Intervention (n =30)	Standard (n =30)	Mean Difference (95%CI)	p value
Protein provided, g/day	94 (27)	58 (12)	37 (26 – 47)	<0.001
	101 [85 – 113]	56 [49 – 64]		
Protein provided, g/kg/day	1.2 (0.30)	0.75 (0.11)	0.45 (0.33 – 0.56)	<0.001
	1.3 [1.1 – 1.5]	0.73 [0.68 – 0.82]		
Protein adequacy, % of estimated requirements	90 (25)	57 (8.0)	33 (24 – 43)	<0.001
	96 [81 – 108]	56 [52 – 63]		
Energy provided from nutrition, kcal/day	1646 (447)	1398 (308)	248 (50 – 447)	0.02
	1754 [1508 - 1971]	1372 [1215-1582]		0.001
Energy provided from nutrition, kcal/kg/day	21 (5.2)	18 (2.7)	2.8 (0.7 – 4.9)	0.01
	22 [20 – 24]	18 [16 – 20]		<0.001
Total energy provided <sup>b</sup> , kcal/day	1835 (340)	1598 (340)	237 (10 – 464)	0.04
	1955 [1639 – 2177]	1545 [1399 – 1858]		<0.01
Total energy provided <sup>b</sup> , kcal/kg/day	23 (5.7)	21 (3.3)	2.5 (0.05 – 4.9)	0.05
	25 [22 – 26]	21 [18 – 23]		<0.001
Energy adequacy, % of prescribed energy	84 (21)	73 (11)	11 (-2.7 – 20)	0.01
	89 [80 – 96]	71 [63 – 81]		<0.001
Estimated protein requirement, g/kg/day	1.3 (0.1)	1.3 (0.1)	0 (-0.05 – 0.05)	1.0
	1.3 [1.3 – 1.4]	1.3 [1.3 – 1.3]		0.85
Estimated protein requirement, g/day	105 (19)	101 (17)	3.6 (-5.7 – 13)	0.44
	104 [92 – 113]	98 [92 – 102]		0.46
Estimated energy requirement, kcal/day	1969 (277)	1918 (255)	51 (-87 – 189)	0.46
Measured energy expenditure, kcal/day (n = 15 per group)	2440 (435)	2194 (718)	246 (-196 – 688)	0.26
Time spent fasting, hours	19 (19)	20 (31)	-0.4 (-14 – 13)	0.94
	12 [3.8 – 34]	7.0 [0 – 19]		0.39
Time to commence enteral nutrition, hours	13 (8)	20 (10)	6.3 (1.6 – 11)	0.01
	13 [7.0 – 18]	17 [12 – 25]		0.01

**Abbreviations:** g, gram; kcal, kilocalorie; kg, kilogram.

<sup>a</sup>Normally distributed values are represented as mean (SD) 95% CI with p values, non-normally distributed values are represented as mean (SD) 95% CI and median [IQR] with p values.

<sup>b</sup>Total energy included nutrition therapy plus energy from propofol and dextrose

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**Table 3.** Nutrition outcomes

<b>Outcomes variables</b>	<b>Intervention<sup>a</sup></b>	<b>n</b>	<b>Standard</b>	<b>n</b>	<b>Risk Ratio (95%CI)</b>	<b>p value<sup>c</sup></b>
Patients with feeding intolerance	9 (30)	30	8 (27)	30	1.1 (0.5-2.5)	0.77
Patient who developed Diarrhea	16 (53)	30	16 (53)	30	1.0 (0.58 – 1.7)	1.0
Malnourished <sup>d</sup> at ICU discharge	2 (6.9)	29	8 (27.6)	29	0.25 (0.06 – 1.1)	0.04
<b>Outcomes variables</b>	<b>Intervention<sup>b</sup></b>	<b>n</b>	<b>Standard</b>	<b>n</b>	<b>Mean Difference (95%CI)</b>	<b>p value</b>
Cumulative incidence of feeding intolerance, days	0.3 (0.5)	30	0.7 (1.5)	30	-0.4 ( -1.0 – 0.2)	0.18
	0 [0 – 1]		0 [0 – 1]			0.86
Cumulative incidence of diarrhea, days	1.9 (2.2)	30	1.3 (1.6)	30	0.7 (-0.4 – 1.8)	0.23
	1 [0 – 3.5]		1 [0 – 2]			0.57
Weight change admission to discharge, kg	-1.3 (8.5)	22	-2.6 (4.7)	19	1.3 (-3.2 – 5.7)	0.57
Mid upper arm circumference change admission to discharge, cm	-1.7 (1.5)	18	-2.0 (1.2)	20	0.3 (-0.6 – 1.2)	0.50
Plasma albumin at discharge, g/L	24 (4.3)	27	24 (5.4)	30	0.5 (-2.6 – 3.7)	0.76

**Abbreviations:** g, grams; kg – kilograms; L, liter.

<sup>a</sup>Proportion values represented as n (%)

<sup>b</sup>Normally distributed values are represented as mean (SD), non-normally distributed data represented as mean SD (95%CI) with p values and median [IQR] with p values.

<sup>c</sup>Pearson Chi-squared p values

<sup>d</sup>Malnutrition defined by Subjective Global Assessment category B or C

**Table 4.** Effect estimate of variables on QMLT (cm) at ICU discharge adjusted for baseline QMLT (cm)<sup>a</sup>

<b>Variables</b>	<b>Effect estimate adjusted for baseline QMLT</b>				<b>Effect estimate adjusted for all covariants</b>			
	<b>Effect</b>	<b>Robust Std.Error</b>	<b>95% CI</b>	<b>P value</b>	<b>Effect</b>	<b>Robust Std. error</b>	<b>95% CI</b>	<b>P value</b>
Baseline QMLT, cm	0.61	0.11	0.38 – 0.83	<0.001	0.56	0.11	0.33 – 0.79	<0.001
Intervention	0.22	0.08	0.05 – 0.39	0.01	0.22	0.08	0.06 – 0.38	0.01
APACHE III <sup>b</sup>	0.02	0.02	-0.02 – 0.06	0.44	0.01	0.02	-0.03 – 0.05	0.70

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Age <sup>c</sup> , years	0.02	0.03	-0.03 – 0.08	0.44	-0.00	0.02	-0.05 – 0.05	0.92
BMI <sup>d</sup> kg/m <sup>2</sup>	0.02	0.09	-0.17 – 0.21	0.82	0.03	0.08	-0.14 – 0.19	0.73
<b>Admission category<sup>e</sup></b>								
Elective	-0.44	0.07	-0.58 – -0.30	<0.001	-0.57	0.08	-0.73 – -0.41	<0.001
Surgery								
Surgical	-0.28	0.08	-0.44 – -0.11	<0.01	-0.24	0.09	-0.41 – -0.06	0.01

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index;

cm, centimetre; QMLT, Quadriceps muscle layer thickness.

<sup>a</sup>QMLT at discharge, mean right and left side measurement have been paired within individuals and adjusted for baseline mean right and left side measurements (n=92)

<sup>b</sup>APACHE III was centered at 75

<sup>c</sup>Age was centered at 60 (per 10 years)

<sup>d</sup>BMI was centered at 30kg/m<sup>2</sup>

<sup>e</sup>Admission category compared to medical admissions

**Table 5.** Functional and other secondary outcomes<sup>a</sup>

Outcome variables	Intervention <sup>a</sup>	n	Standard	n	Mean Difference (95%CI)	p value <sup>c</sup>
Handgrip strength (best), kg	20 (6.1)	6	21 (9.3)	16	-0.34 (-9.0 – 8.3)	0.94
Muscle strength (MRC score)	55 (5.9)	7	52 (9.6)	14	2.6 (-5.8 – 11.0)	0.53
Physical Function <sup>e</sup>	6.8 (3.8)	8	7.9 (3.4)	14	-1.1 (-4.4 – 2.2)	0.49
ICU LOS, days	10.6 (8.3)	30	9.1 (5.5)	30	1.5 (-2.2 – 5.1)	0.42
	7.8 [5.9 – 13.4]		7.5 [4.9 – 12.7]			
Hospital LOS, days	27.4 (19.0)	30	18.8 (10.9)	30	8.6 (0.6 – 16.6)	0.04
	22 [9.9 – 43]		15 [9.9 – 25]			
Length of MV, days	8.7 (7.5)	30	7.0 (5.0)	30	1.7 (-1.6 – 5.0)	0.30
	6.2 [4.5 – 10.8]		5.1 [3.6 – 8.5]			
Outcome variables	Intervention <sup>b</sup>	n	Standard	n	Risk Ratio (95%CI)	p value
ICU acquired weakness <sup>d</sup>	1 (14)	7	4 (28)	14	0.5 (0.07 – 3.7)	0.47
Renal failure <sup>f</sup>	3 (10)	30	3 (10)	30	1.0 (0.22 – 4.6)	1.0
Mortality 28 days	4 (13)	30	5 (17)	30	0.8 (0.24 – 2.7)	0.72

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Mortality 60 days	4 (13)	30	5 (17)	30	0.8 (0.24 – 2.7)	0.72
Discharge to a rehabilitation facility	12 (40)	30	13 (43)	30	0.9 (0.51 – 1.7)	0.77

**Abbreviations:** Kg, kilogram; LOS, length of stay; MRC, Medical research council score;

MV, Mechanical ventilation

<sup>a</sup>Normally distributed values are represented as mean (SD) 95% CI with p values, non-normally distributed values are represented as mean (SD) 95% CI with p values and median [IQR] with p values.

<sup>b</sup>Portions are listed as n (%)

<sup>c</sup>Pearson Chi-squared p values

<sup>d</sup>ICU Acquired weakness defined as MRC score < 48

<sup>e</sup>Physical function, measured using Physical function in ICU Test –Score

<sup>f</sup>Renal Failure defined using the RIFLE criteria

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