Author’s response to reviews

Title: Targeted Full Energy and Protein Delivery in Critically Ill Patients: A study protocol for a pilot randomised control trial (FEED Trial)

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Author’s response to reviews:

11th January 2018

Professor Andrew Hayen

Editor

Pilot and Feasibility Studies

BioMed Central

Floor 6, 236 Gray's Inn Road

London

United Kingdom
Dear Andrew Hayen,

Re: Pilot and Feasibility Studies manuscript number PAFS-D-17-00109

‘Targeted Full Energy and Protein Delivery in Critically Ill Patients: A study protocol for a pilot randomised control trial’

Thank you for your email dated 21st of December 2017. On behalf of my co-investigators we thank the reviewers for their constructive comments.

We believe that we have addressed all of the issues raised and that the suggested modifications have greatly enhanced the manuscript. We are more than willing to consider further changes should these be requested.

All additions to the manuscript have been included in red font and deletions marked with a strikethrough. In particular, the following issues have now been addressed:

Reviewer Comments:

Reviewer #1:

Background

Query1# Line 67, first paragraph, last sentence ‘(1.5g/kg/d) was associated with a reduction in mortality…’ would need to be referenced.

Response: We agree and an appropriate reference has been added.

Query2# Line 91-93. Sentence absolutely fine as it is, or you could consider writing: ‘…to quantify starting muscle mass and characterize muscle loss in the critically ill.’

Response: We have considered this change however have decided to leave the text as it has been written.
Query 3# Line 115, typo: 'including a of lack' should be including a lack of…

Response: We agree and this has been corrected.

Baseline data collection:

Query 4# Line 172, 'baseline measures to reflect status of patient at or prior to randomisation'. My question relates to the Katz Index: do you ask a proxy to complete this for pre-ICU admission? Or if interested at the point of randomisation I imagine the score will always be zero as the Katz Index has a substantial floor effect?

Response: The reviewer is correct, a proxy will be asked in order to complete this assessment, relating to their function prior to the ICU admission. We acknowledge that the assessment of function after ICU is challenging and have made the following adjustment in the text:

Baseline measurements will reflect the status of patients at or prior to randomisation. Demographic data includes admission diagnosis, comorbid illness including quantification using the Charlson Comorbidity Index (29), Katz Activities of Daily Living (ADL) index (30) (prior to the ICU admission), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and admission Sequential Organ Failure Assessment (SOFA) Score.

Query 5# Would the investigator performing the SGA be trained in the technique?

Response: The SGA will be performed by a Dietitian who has received considerable training and is experience with using this technique. The follow adjustment has been made to the manuscript:

Line 183: Baseline measures, collected by the study Dietitian, include height (using ulna length (31)) weight (from bed scales), Body Mass Index (BMI), mid upper arm circumference, nutritional status using the subjective global assessment (SGA) (32, 33),

Query 6# Would the independent dietitian be using predictive equations, if so which one(s)?

Response: Yes, participants will receive standard care for our institution, which is reflective of practice across Australia, the Dietitians utilize both weight based equations or the Schofield equation. The following adjustment has been made to the text:

Line 187: independent dietitian estimation of energy (weight based or Schofield equation (34))
Query 7# Table 3 data collection: We used some similar outcome measures in a fairly recent study (publication in progress). Our planned outcome measures (including muscle ultrasound) around the day 14 mark were minimal, N=17 from 80 recruited patients due to deaths/discharges/drop-outs. If you haven't started your data collection yet, could some of your time points be brought forward, e.g. days 1, 5, 7, 10 or as per Puthucheary et al (JAMA) days 1, 7, 10 whilst still keeping the ICU discharge time point? For our study mean ICU LOS was much lower than anticipated, 5 days. Please ignore this comment if already recruiting.

Response: We very much agree that drop-outs are a major issue in critical care research, particularly for trials of nutritional interventions. While we acknowledge that it may have been useful to collect more frequent measurement earlier, when designing the trial it was not feasible with the resources available. We included days 1, 5, 10, 15 and discharge based on the Puthucheary study. We have now completed enrolment and so cannot adjust our time points for this trial.

Query 8# Standard Care group:

Line 205, this is just a point of interest. Why would one of your feeds be sourced from China and the other the Netherlands if both are from Nutricia?

Response: According to the information provided to us from Nutricia this is the source of the different products for our market.

Primary Outcomes:

Query 9# Line 279, do you use citrate regional anti-coagulation in CRRT at all? If you do then calorie contribution from the citrate would have to be incorporated too.

Response: In our facility we do not routinely use citrate in CRRT and therefore we have not included this.

Secondary outcomes:

Query 10# Would it be worth adding plasma urea as an outcome measure, particularly as one of the groups will be receiving a higher protein dose? The recent EAT-ICU study incorporated this outcome measure (including reducing protein load if plasma urea > 20mmol/L.)

Response: We agree and this data was collected in the study. The following sentence has been added.
Line 312: The presence of acute renal failure defined by the RIFLE criteria (41) and plasma urea and creatinine levels will be assessed on a daily basis.

Query 11# With your muscle ultrasound protocol, would it be worth stating what you would do to ensure that the exact same landmark on the leg is measured for repeated measures of each patient? We used permanent marker and Tegaderm to ensure that we measure over the exact same place and that our markers weren’t washed off in-between measurement days. Will you be reporting intra-rater reliability for the investigator using the muscle ultrasound technique?

Response: We agree that the consecutive measurement of muscle is challenging, we have also used a permanent marker and confirm the position with a tape measure from the top of the patella if this is no longer visible. We have not planned to test intra-rater reliability as other groups, using larger numbers, are doing very good work in this area. The following has been added.

Line 296: The measurement will be completed on all participants, with bilateral measurements at two points; the midpoint between the Anterior Superior Iliac Spine (ASIS) and the upper pole of the patella and at the point two thirds between the ASIS and the top of the patella (19-21), the landmarks will be marked using a ‘permanent’ pen.

Power calculation and randomisation

Query 12# If your study is powered for 29 participants per group, would it be best to recruit and randomise more than 60 patients in order to account for deaths, drop outs etc?

Response: We agree that greater numbers, particularly during exploratory work such as this trial, would be useful. However, we are limited with the resources available.

Reviewer #2:

Abstract:

Query 1# Line 43: A secondary outcome includes change in quadriceps muscle layer thickness at ICU discharge; please include the baseline measure for which the change is deduced (e.g. ICU admission, within 24 hours of enrolment, etc)

Response: This has been added in the abstract.
Secondary outcomes include change in quadriceps muscle layer thickness (QMLT) from baseline (prior to randomisation) to ICU discharge and other nutritional and patient-centred outcomes.

Background:

Query 2# Paragraph 1: Given that increased energy delivery is a co-primary outcome, please provide justification of why this is significant/important, as has been done for protein. The way the first paragraph stands, it reads as though a change in energy delivery is a secondary, rather than a co-primary outcome.

Response: We agree and have modified the manuscript. Whilst the focus of the trial is to achieve a clinically significant increase in protein delivery with the intervention, we included energy as a co-primary outcome due to the nature of the intervention - a volume based feeding regimen - that may reduce energy delivery.

Page 3 line 57-59

Prominent critical care nutrition guidelines recommend that protein should be provided at a level of 1.2-2.0 g/kg/day, with possibly higher amounts for patients with multi-trauma, obesity and burns, and greater than 80% of energy targets should be met (1); however, there is a lack of high-quality evidence to support these guidelines (2).

Page 3 line 70

In addition data from a prospective observational cohort study from a single centre suggested that the provision of more protein (greater than 1.5 g/kg/day) was associated with a reduction in mortality when adjusted for severity of illness and age (6). Finally, observational study and preliminary trial data supporting the concept that increasing calorie delivery will improve outcomes (7-9).

Query 3# Lines 67-69: Please provide a reference for the mentioned prospective observational cohort study.

Response: This has been addressed in Query 1# for Review 1.
Query 4# Lines 78-84 are confusing. Are you suggesting that a volume-based approach is unlikely to increase energy and protein delivery due to regulation of gastric emptying? This appears to contradict the purpose of your study. Are you able to explain this with a link back to the study proposed? I also think that as you are not measuring gastric emptying that your study will not actually be able to address whether volume-based feeding leads to an increased absorption of calories/protein.

Response: The purpose of this section is to highlight the uncertainty (we hope the intervention increases protein delivery but this is not assumed) and therefore emphasises the need to undertake a pilot trial. We agree that we could have made this clearer and we have made the following adjustment in the text:

However, theoretically volume based feeding protocols with protein supplementation may not achieve greater delivery of protein and energy to patients due to issues with feeding intolerance, as increased nutrient delivery, particularly protein, to the small intestine, stimulates the feedback loop to slow gastric emptying (9)(10). Therefore this approach may inadvertently decrease protein and energy delivery.

Query 5# Lines 105-108: Please explain what you mean by 'reduced protein loss'; how was this measured?

Response: This is referring to total body protein loss, which was measured in this study. The following adjustment has been made.

A retrospective observational study of 106 critically ill patients, by Ishibashi and colleagues, reported that protein intake above 1.5g/kg/day substantially reduced total body protein loss when compared to those who receive less than 1.1g/kg/day (24).

Query 6# Line 115: Please edit to read 'a lack of' rather than 'a of lack'.

Response: This has been addressed in Query 3# for Review 1.

Study objectives:

Query 7# The secondary objectives require refining. Objectives I and II assume that increased nutrient delivery will improved mid upper arm circumference and malnutrition incidence, and that change in quadriceps muscle layer thickness will improve muscle strength, physical function and incidence of ICUAW. I think these objectives should be separated to ensure there is one outcome per objective.
Response: We agree and we have made the following adjustment to the secondary outcomes.

I. Improves overall protein and energy adequacy without increasing feeding intolerance or diarrhoea.

II. Improves nutritional related outcomes including the incidence of malnutrition at ICU discharge or weight loss or mid upper arm circumference change from baseline to discharge.

III. Decreases the change in quadriceps muscle layer thickness (QMLT) from baseline to ICU discharge.

IV. Decreases the incidence of ICUAW or alters muscle strength or physical function scores.

V. Alters the duration of the ICU admission, number of deaths and the requirement for discharge to a rehabilitation facility.

Query 8# It is unclear how the tertiary objective differs to the listed secondary objectives.

Response: We agree that these are probably covered in the secondary outcomes and therefore we have decided to delete these.

Methods/Design:

Query 9# Line 164: How will the patient be deemed competent to provide their own consent (e.g. by the treating medical team)?

Response: This will be determined by the principal investigator in liaison with the treating physician and the person responsible.

Query 10# Inclusion criteria in Table 1: how is 'no immediate plans to extubate' defined (e.g. 4 hours, 24 hours)?

Response: This has been added in the text.

Mechanically ventilated (MV) for ≥ 48 hours with no immediate plans to extubate in the next 24 hours
Query 11# The outcome of quadriceps muscle layer thickness is open to measurement bias if thickness is measured by the investigator. How will this be accounted for given the study is single-blinded only?

Response: We agree that this is a limitation of our trial and ideally all assessments would be completed by a blinded assessor. However due to limited resources available, with the training required and the time it takes to complete these measurements, and that this is not the primary outcome, the principal investigator had to complete these assessments. However the baseline assessments are completed prior to randomisation to limit bias.

Query 12# Greater energy delivery is an outcome of the study, however, the protocol is written like it is anticipated that the arms will be isocaloric, particularly on page 8. Please amend to state that while the standard care arm will be prescribed 25 kcal/kg, it is not anticipated that they will actually receive this.

Response: This has been added and the following adjustment has been made:

This strategy is designed to prescribe 1.0g/kg protein and 25 kcal/kg of energy per day, however it is anticipated participants will receive less than this due to interruptions to nutrition therapy (36).

Query 13# The intervention arm will receive additional protein powder. How will the additional calories provided from this powder be accounted for?

Response: We have not made adjustments for this; it is likely to be less than 100kcal/day, which may not be clinically significant.

Query 14# Given the additional protein will be provided to the intervention arm in a bolus fashion, as opposed to continuously, please comment on the influence this may have on protein digestion, absorption, and intake into muscle.

Response: The protein will be given in 6g boluses, 2-4 times per day, depending on the amount required. This may delay gastric emptying as protein is a potent simulant to the small bowel intestinal feedback loop, however we will be assessing gastric residual volumes to assess if there are any difference between groups. It has been shown that bolus protein administration of approximately 25g may benefit muscle protein synthesis, however the boluses in our study will be much smaller, therefore it is unclear if the bolus size would be sufficient to have this effect. This will need to be considered when generalizing to continuous delivery of higher protein formulas.
Query 15# Will fluid delivery between the two groups be controlled, particularly given additional water may be required in the intervention arm to deliver the protein powder?

Response: Fluid delivery has been somewhat controlled for because the standard care arm will receive 1.0kcal per ml formula, which will delivery greater fluid to meet the energy target compared to the intervention using 1.25kcal per ml formula, however the intervention will receive additional fluid with the protein flushes. In addition we have collected daily fluid balance and therefore we can assess if there are any differences between the groups.

Example: 70kg patient: 25kcal/ml = 1750kcal

Standard care: 1.0kcal/ml = 72ml/hr for 24kcal = 1728ml/day of formula

Intervention: 1.25kcal/ml = 58ml/hr for 24/24 = 1382 ml/day of formula

Additional protein = 18 g (3 x 60ml water) = 180ml

Total fluid = 1562ml

Query 16# Page 11, Secondary outcomes: Please include details of the ultrasound transducer to be used.

Response: The following adjustments have been made.

A portable ultrasound device (Sonosite S-ICU™) with a multiple frequency transducer (13-6MHz, 6cm) will be used to obtain muscle mass images.

Query 17# Sample size calculation: At which time-point is the mean difference of 0.5 cm in QMLT between the two groups expected? It is unclear how this sample size calculation has been performed if using a mean (SD) of QMLT only. At what time-point was the mean QMLT from the VALIDUM study taken? If mean QMLT thickness is only 1.3 cm, an expected difference between the two groups of 0.5 cm seems ambitious. Change in QMLT has been reported in ref 19, albeit at different time-points.

Response: Thank you for this question, the sample size for this study was based on the provision of protein, not quadriceps muscle layer thickness (QMLT). Observational data collected in our unit showed a mean daily protein delivery of 50.8 g/day with a SD of 20.1 g. Using these estimates, to detect a difference in mean protein delivery of 15g between 2 groups with 80%
power at an alpha of 0.05 would require a sample size of 29 participants in two equally sized groups (overall 58 patients).

As a secondary calculation for a study of that size, we used the average (SD) results for QMLT collected within 72 hours of CT scan assessments (themselves performed in a 4-day window around the time of ICU admission) reported in Table 2 of Paris et al JPEN 2017;41:171-180. These published QMLT estimates (1.3 cm ± 0.6 cm) suggested that a study of two groups each of 29 patients would have a little over 80% power at an alpha of 0.05 to detect a difference of 0.5 cm between the mean QMLT across groups. We acknowledge that it is difficult to directly compare these data to the present study protocol and agree that a mean QMLT difference of 0.5 cm is ambitious as a clinical effect. However we felt it potentially useful to provide some indication of the mean QMLT difference that would be detectable with reasonable power given the current study sample size.

Query 18# The intervention is a daily volume-based feeding rate and standard care is an hourly rate-based feeding protocol. Given this, the two groups have potential to receive different amounts of calories. Therefore, it will not be possible to separate out effects of calories versus protein on outcomes, and you will be unable to attribute any potential benefits with the intervention to protein or calories. Why did the authors choose not to focus on protein alone, given the background provided, and the discussion, concentrate on protein delivery.

Response: We agree that this is a limitation of the study. We are testing an intervention rather than providing definitive evidence as to the optimal protein (or energy) that should be delivered. It is however, expected that the intervention will result in substantially greater differences in protein delivery than energy delivery between the two groups.

Discussion:

Query 19# Given functional patient-centred outcomes have not been powered, I would exclude this from the final statement on line 403.

Response: We agree that any differences in these outcomes are unlikely to represent a true difference. However, we believe it is essential that we present these data, but that we report these in a circumspect manner and wish to present these data as preliminary estimates. Therefore the following adjustments have been made.

This pilot study aims to clarify whether an enteral feeding protocol with a volume target and supplemental protein has potential to increase protein and energy delivery in mechanically-
ventilated critically ill patients, and will provide preliminary estimates as to whether this intervention has the capacity to affect muscle mass or other patient-centred outcomes

References:

Query 20# Reference 18 is incomplete.
Response: This has been rectified.


Query 21# Reference 31 requires amending.
Response: This has been rectified.


The following reference has also been amended.


Once again, we thank you and the reviewers for the constructive comments and we believe that we have addressed all of the issues raised and that the suggested modifications have greatly enhanced the manuscript.

Yours Sincerely,

Kate Fetterplace