Reviewer’s report

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

Version: 0 Date: 19 Nov 2017

Reviewer: Lee-Anne Chapple

Reviewer's report:

Overall:

This manuscript is a protocol for a randomised controlled pilot study on the ability of a high protein volume-based feeding regime to deliver more calories and protein than standard care. Overall, the manuscript is very well written and the aims are clear. The study design is complex, the data collection ambitious, and the outcome of importance to the critical care field.

Abstract:

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)

Background:

1. 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.

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

3. 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.
4. Lines 105-108: Please explain what you mean by 'reduced protein loss'; how was this measured?

5. Line 115: Please edit to read 'a lack of' rather than 'a of lack'.

Study objectives:

1. 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.

2. It is unclear how the tertiary objective differs to the listed secondary objectives.

Methods/Design:

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

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

3. 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?

4. 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.

5. The intervention arm will receive additional protein powder. How will the additional calories provided from this powder be accounted for?
6. 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.

7. 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?

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

9. 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.

10. 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.

Discussion:

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

References:

1. Reference 18 is incomplete.

2. Reference 31 requires amending.

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