Reviewer’s report

Title: Tittle: Comparison of the effect of three different protein content enteral diets on serum levels of proteins, nitrogen balance and energy expenditure in critically ill infants: study protocol for a randomized controlled trial

Version: 0 Date: 05 Jul 2019

Reviewer: Nilesh Mehta

Reviewer's report:

Trials review

Thank you for the opportunity to review this protocol.

I believe the topic of optimal protein dosage during acute critical illness to be ripe for investigation. The authors propose a trial that will add to the feasibility of achieving high protein delivery in the population of interest.

The authors propose their RCT, with 3 arms, to be conducted in 3 centers.

Their main objective is to examine the impact of protein-enriched infant formula on serum levels of total proteins, albumin, prealbumin, transferrin, retinol, nitrogen balance, and energy expenditure; in children under 2 years of age, on enteral nutrition, with expected stay of at least 72 hours in the PICU. A secondary objective is to examine the secondary effects of administering protein-enriched diet.

Major comments:

1. The study proposal was approved by local IRB in 2010. I am not sure why the study has not enrolled any patients until 2019. If there were attempts to enroll, prior study results, changes in protocol since 2010, etc; these findings, observations, experience and rationale for this protocol submission in 2019 must be reported/discussed by the authors.

2. As pointed out above, please discuss the differences (if any) between the protocol reported in Clinical trials.gov and the current submission.

I have the following questions about the study design:

3. Please provide a clear hypothesis for each aim.

4. Please explain the rationale for limiting the study to children under 2 yrs pf age.
5. I understand that patients on PN were excluded, as the study is only exploring the impact of protein supplementation enterally. Do the authors have enough patients in the 3 PICUs who would qualify for the study and therefore complete the study in time? Was this relevant to the delay in study starting after 9 years of initial study protocol approval.

6. Please explain what is meant by Protein levels?

7. Please explain how protein metabolism will be defined. Currently the authors state that protein (amino acid) levels and nitrogen balance will be measured. How will this equate to metabolism? How will serum levels of albumin, prealbumin and RBP equate to protein metabolism. These concepts and definitions for metabolic states must be clarified. Also, important to state these in the form of the hypothesis.

8. Enrollment: When will enrollment be completed? Is there a limit after admission, before which enrollment should be achieved?

9. I appreciate the inclusion of pts with LOS>72 hrs. What is the average/median length of stay for patients in these PICUs? Will there be meaningful exposure to study treatments? Again, do the authors think they have the numbers needed to complete this trial?

10. Thank you for including the details of EN initiation and advancement. Is this protocolized in all 3 institutions? Are definitions of intolerance uniform across the units?

11. What is the current expectation of indirect calorimetry at these sites? All 3 have the capability? What do the authors expect in terms of percentage with IC versus estimated caloric goals?

12. Please explain the rationale for aime#3; impact of protein supplementation on energy expenditure.

13. Please explain study end criteria # 4. What is hypercatabolism? How is renal function disturbance defined?

Statistical analysis:


Minor comment:

Please change A.S.P.E.N. to ASPEN throughout the manuscript.
Overall, this is an important study and the results will add significantly to literature on a subject that deserves further investigations. The current proposal requires addition of further details to clarify study methodology.

**Level of interest**
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An article of importance in its field

**Quality of written English**
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Acceptable

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**Statistical review**

Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.
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