Author's response to reviews


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Author's response to reviews: see over
To the editors and the reviewer, dr. Gordon Doig,

Dear Sir,

We thank the reviewer for the positive comments and very constructive remarks on our manuscript "A randomized controlled trial on the impact of early parenteral nutrition completing enteral nutrition - EPaNIC trial - in adult critically ill patients Protocol version EPaNIC 2007 1-2-2. Study protocol and statistical analysis plan". We addressed all comments and adapted the manuscript accordingly. While editing this revised version we changed the manuscript to double line spacing conform to the journal style. When addressing the changes we made, we will refer to the new page numbers in the revised manuscript.

1. The reviewer correctly comments that our plan doesn’t mention the test that will be used to detect interaction between the study intervention and the subgroups studied in the subgroup analysis. He also suggests specifying the p-value that will be used to judge whether subgroup differences might be meaningful, since these analyses will have a lower power.

We addressed this important issue in a paragraph added on page 19. “These a priori defined subgroup analyses will be performed for the primary and safety endpoints without correction for other variables. To test for interaction between the identified subgroups and the studied intervention, a multivariable analysis (logistic regression or proportional hazard analysis as appropriate) will be performed for each subgroup variable separately and with the subgroup variable, the intervention and their interaction in the model. The interaction will be tested at a significance level of 0.1.”

2. The reviewer alerts us to the fact that the planned 90 day mortality analysis in the intention to treat population including patients discharged from the hospital isn’t explicitly mentioned in the section Safety Endpoints.

This important outcome analysis is part of our plan and we changed the manuscript accordingly on page 20. “Safety endpoints comprise vital status (mortality 90 days after randomization independent of ICU and hospital discharge status, hospital mortality, ICU mortality and proportion of patients discharged alive from ICU within 8 days) hypoglycemia, serious adverse events and complications related to the mode of nutrition. Survival up to 90 days after randomization in both treatment groups will be compared by Kaplan Meier survival plots. The impact of “late PN” versus “early PN” will be analyzed, with and without correction for age, BMI & NRS categories and type and severity of illness, by Cox proportional hazard analysis. Vital status up to 90 days predictably will be traceable for virtually all patients via the National Registry, loss to follow-up will likely not be present except for some patients who will have a residence outside the Belgian territory. In addition, we will record vital status at ICU and hospital discharge and 90 days after randomization, and will analyze differences with Chi-square testing. All analyses will be performed in the intention to treat population."
3. Finally, the reviewer suggests reporting the completion date rather than the “current recruitment” of the trial.

   This has been removed as requested from p 3 and p 25. We replaced this section by: “The study has been initiated as planned on August 01 2007. One interim analysis advised continuation of the trial. The study will be completed in February 2011.”

4. While revising the manuscript we remarked a typographical error on page 24. Distribution of 6 MWD will be assessed at hospital discharge rather than at ICU discharge, as wrongly stated.

   We apologize for this mistake and corrected it. “Distribution of 6 MWD at hospital discharge in both groups will be compared,...”

We thank the editors for their interest in our manuscript and the referees for the dedicated review.

Sincerely yours,

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