Author's response to reviews

Title: Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial

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Author's response to reviews: see over
Reply to the Reviewers’ comments

Manuscript

Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial

We would like to thank the editors and the referee for thoroughly reviewing our manuscript and for the constructive comments to improve it further. All the comments have now been addressed and the adaptations have been included in the revised version of the manuscript.

Please find below our point by point replies to the comments.

SPIRIT Checklist

Administrative information

Protocol version:

3 Date and version identifier

Reply: Adapted as requested. The full protocol is stored centrally and identified with a unique number by the sponsor. For each amendment, the amended protocol received a new version number after approval by the ethical committee and is also stored centrally in Leuven. The current final version has the number ML8052 Amend-ID0005. This is now mentioned in the manuscript on page 8.

Roles and Responsibilities:

5b Name and contact information for the trial sponsor

Reply: Adapted as requested. This is now mentioned on page 2. The sponsor is KU Leuven.

Introduction

Trial design

8 Description of trial design including type of trial allocation ratio, and framework
Allocation ratio 1:1 Parallel group—not stated. Superiority study—not stated.

Reply: Adapted as requested, see pages 7, 9 and 10.
Methods: Participants, interventions, and outcomes

Interventions

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease).

Reply: Adapted as requested. We have added on page 14 the following:

“Criteria for stopping the study intervention:

When in the intervention arm (late PN group), blood glucose concentration falls spontaneously (without exogenous insulin) below 50 mg/dl, the standard infusion of glucose 5% is switched to 10% glucose until blood glucose concentration is higher than 80 mg/dl and stable. Thereafter, the infusion of glucose 10% is stopped again and switched back to glucose 5%”.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Reply: Adapted as requested. On page 13 we have now added the following information:

“Adherence to the protocol in Leuven and Rotterdam was guaranteed by using a PDMS guided system and by careful follow-up by study nurses. In Edmonton, a paper protocol was used and adherence checked by an independent study nurse and physician.”

Further information on this aspect was already given in the section “trial organization” on page 19. (now highlighted)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 20, 21 One-sided?

Reply: Based on the adult EPaNIC trial and mechanistic studies we hypothesized that early PN is harmful. Information on how the sample size was calculated was already mentioned on page 22. Given this prior information from the adult study, we decided that a 70% power two-tailed was sufficient in the face of an 80% one-tailed power.

We slightly adapted the section, and highlighted it in the revised version, in order to further clarify this.

“In the design phase of the PEPaNIC trial, and based on the previous adult EPaNIC trial results, the sample size (N=1440, 720 patients per arm) was determined in order to detect a reduction in the incidence of new infections during PICU stay from 20% to 15% (Absolute Risk Reduction 5%), with at least 80% one-tailed power and at least 70% two tailed power and at an alpha error of 5%. With this sample size, the trial can also detect a major safety issue, such as a doubling of the PICU mortality rate from 4% (the baseline mortality in the Leuven center) to 8% with a statistical power of 89% in a two-sided test with an alpha error of 5%.
Two interim analyses of the safety endpoints (except 90 day mortality) only were planned (after inclusion of 480 upon specific request of the DSMB, and after inclusion of 50% of the study population).

**Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size?**

*Reply: Adapted as requested. We have now added, on page 20, the following:*

“In order to achieve adequate participant enrolment to reach target sample size, regular meetings and site visits take place every 3 months together with the Rotterdam team and via teleconferences with the Edmonton team.”

**Methods: Data collection, management, and analysis**

**Data collection methods**

**18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols**

*Reply: Adapted as requested. We have now added the following on page 21, where mentioning the consort diagram:*

“For the primary and secondary endpoints taking place during PICU stay all data will be available. In case of request for discontinuation of the study intervention by patients, parents or legal guardians, this will be respected, but all data will be analyzed. In case of consent withdrawal, the parents will be asked whether the data can be used for analysis. In case this would not be allowed, all data of that patient will be removed from the database, and this will be reported in the consort diagram. At all time, the intention to treat principle will be respected and reported. For none of the acute primary and secondary outcomes, data imputation will be done.”

**Statistical methods**

**20a Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**

*Reply: All statistical test that will be used are described on pages 21-22.

**20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)**

*Reply: Adapted as requested. At all-time the intention to treat will be respected. No data imputation will be done, which is now mentioned on page 21.*
Monitoring

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.

Reply: Adapted as requested.

We added on page 20:

“Regular data auditing is done by the administrative trial team, the DSMB and by the central independent audit procedure in place at the University Hospital of Leuven in compliance with the European Trials Directives.”

Ethics and dissemination

Consent or assent

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Reply: Information provided as requested. All the information about the trial is written in the informed consent form. Patients or their legal guardians have to sign separately for each biological specimen that will be collected and evidently can refuse the collection of a specific specimen.

We have now provided the following information on page 8:

The study protocol and (deferred) informed consent forms were approved by the institutional ethical review boards in Leuven BE (ML8052 Amend-ID0005), Rotterdam NL (NL38772.000.12) and Edmonton CA (Pro00038098). Informed consent is given in writing by the parents or the legal guardians, confirmed by the child when older than 7 years, after providing all information orally in plain language and in writing. For planned admissions, informed consent is obtained prior to surgery/procedure. For unplanned admissions, informed consent is obtained within 24 hours after admission on the PICU (deferred informed consent as the nutritional therapy should be initiated from PICU admission onward).

Confidentiality

27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Reply: We have now provided the following information on page 19:
“All data are stored anonymously. Investigators involved in the trial do not have direct access to the database. In addition, the study monitor has logged the use of the database. After the trial, the study monitor will store all data in a secured file that is only accessible by the study monitor himself.”

**The TIDIER Checklist**

3. **Materials:** Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).

Reply: This information is now provided as requested, on page 8;

Informed consent is given in writing by the parents or the legal guardians, confirmed by the child when older than 7 years, after providing all information orally in plain language and in writing. For planned admissions, informed consent is obtained prior to surgery/procedure. For unplanned admissions, informed consent is obtained within 24 hours after admission on the PICU (deferred informed consent as the nutritional therapy should be initiated from PICU admission onward).

5. For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.

Reply: Adapted as requested. The following information was now provided on page 13:

“The medical and nursing staff of the pediatric intensive care unit were all informed and trained extensively during regular meetings before the start of the trial and were familiarized with the protocol. In order to optimize protocol compliance, the protocol was programmed in the patient data management system. The use of this program was explained to every nurse, trainee and resident on the PICU and was always supervised by the senior staff.”

7. Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.

Reply: This information is provided. Three tertiary referral hospitals are involved in the trial, as mentioned on page 11-13. All interventions were done within the PICUs of these hospitals, as is clearly described throughout the manuscript.

Other small changes in the manuscript are highlighted.