Author's response to reviews


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Author's response to reviews: see over
To:
Editor-in-Chief
Trials

Nîmes, 13 June 2014

Dear Editor-in-Chief,

Please find enclosed the revised version of our article entitled “Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: The IDEAL-ICU study (Initiation of Dialysis EArLy vs delayed in the Intensive Care Unit): Study protocol for a randomized, controlled trial.”, which we would like to re-submit for your consideration.

We would like to thank the reviewer for the constructive comments, and we have addressed all these points in the revised version. Our point-by-point responses are outlined below.

We hope that you will now find our work suitable for publication, and we look forward to hearing from you soon.

Thank you and kind regards,

Dr. Saber Davide Barbar
On behalf of all authors

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1. Will the study design adequately test the hypothesis?
The primary objective is to assess whether the timing of renal replacement therapy initiation (early vs. delayed) has an impact on mortality at 90 days in patients with acute kidney injury in septic shock. This is an appropriately designed and described RCT, which will address this research question.

Thank you.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

It is recommended that protocols contain information as outlined in SPIRIT guidance. There is sufficient detail on the majority of components of the study, which would allow replication. However, there are a few sections where some further clarification would be useful, and the protocol would benefit from re-ordering of some sections to help the reader:

- The RIFLE classification is being used to assess eligibility of patients for inclusion, which seems appropriate. These criteria are mentioned a few times before there is adequate reference to the guidance. In ‘study design’ section, Pg 6, the guidance should be referenced or a statement should be added making it clear that the criteria are fully explained in the ‘study definitions’ section.

The reference to the original publication of the RIFLE criteria is included at the first mention of the RIFLE classification (1st line of the objectives, page 5). As the reviewer suggested, we have also specified here that further details are given in the “study definitions” section. The same has been done in the study design section (page 6, 1st paragraph of the methods section, line 4).

– There is limited discussion about the consent process, and so there is some ambiguity about when patients consent, and if they are not able to due to incapacity how a legal/personal representative will be approached. Information should be added to the ‘Trial Protocol’ section before randomization, and/or a full explanation should be provided as part of the ‘ethical considerations’.

When patients meet the inclusion criteria, and do not present any non-inclusion criteria, they are informed (orally, with supporting documentation in written format) about the study by the investigators, and invited to participate. Study information includes: study objectives, duration of participation, procedures that will be implemented during the study, expected benefits, foreseeable risks, any adverse effects that could result from the treatment or examinations performed in the course of the study, data confidentiality, and study insurance. If the patient is temporarily or permanently incapable of receiving the appropriate information or making an informed decision regarding consent to participate, the patient can still be included if informed consent is given by the patient’s surrogate or legal representative, or a close relative if no legal representative has been designated. If the patient subsequently regains the capacity to understand the study procedures and provide informed consent, their consent must be obtained. Patients can be included in emergency situations if their condition precludes consent and no legal representative or close relative is available to provide consent. In this case, the investigator notes and justifies in the patient’s medical record that
the patient was temporarily unable to receive the study information and provide informed consent, and that no legal representative or close relative could be reached (indicating the telephone numbers that were used to try to reach any relevant representatives, and the times of the calls). Written consent must subsequently be obtained from the patient, as soon as their clinical status allows.

A slightly shortened version of this text has been included in the “Trial Protocol” section, in a new paragraph entitled “Informed Consent”, before “Randomization”, as suggested by the reviewer.

Description of study flow would benefit from a schematic diagram, in the form of CONSORT, to include patient numbers in each group

A flow chart of the study has been included as a figure. The number of patients to be assigned to each group has been indicated.

The exact numbers who actually receive treatment in each arm, as well as the number of those who complete follow-up will only be available at the end of the study.

The sample size calculation section would be better earlier in the protocol as otherwise it is not clear how many participants are required, or how this works within the patient flow. In the ‘Trial Protocol’ section, this could be placed before randomization.

The sample size calculation section has been moved to the start of the “Trial Protocol” section, before “informed consent” and “randomization”, in order to make it clearer how many patients will be involved.

Some further clarification on how the decision on the assumed reduction in mortality was chosen would help justify the sample size. Is a 10% reduction based on previous data (in which case reference this), or chosen as a clinically relevant difference by the study team?

As the reviewer correctly surmised, the choice of a 10% reduction in mortality was made by the study team, on the basis that it represents a clinically relevant difference.

There are currently no data in the literature that could serve as a precedent for this, due to wide variations between existing studies in the types of patients included, the definitions of AKI used, and the definition of what constitutes early or late treatment. Most studies are observation or retrospective, and reports range from no benefit of early dialysis (Bouman Crit Care Med 2002), to a small benefit dependent on the parameter chosen to differentiate early vs late (creatinine or urea or time since admission) (Bagshaw J Crit Care 2009), to a more considerable benefit (Elahi Eur J Cardiothor Surg 2004). In view of these heterogeneous data, a conservative estimate of a 10% reduction was retained as being clinically relevant, yet not overly optimistic. In addition, from a methodological point of view, estimating a 10% reduction leads to a sample size that is feasible, in light of the recruitment capacities of the participating centres, and the human and financial resources available for the study.

We have added this a short discussion of this point at the end of the paragraph on sample size calculation.
The randomization process is described in reasonable detail, but there is no mention of the allocation ratio (presume 1:1 from later sample size description) and no mention of blinding. It is likely that blinding is not possible due to the nature of the intervention, but it would be useful to state this and make it clear to the reader that this can’t be achieved in the study.

The reviewer is again correct in surmising that the allocation ratio is 1:1. Again, as the reviewer correctly notes, blinding is not possible due to the nature of the intervention, but the CIC-EC (Dijon) will manage all the data and generate blinded reports for the data and safety monitoring board. The clinical coordination team and the investigators at the participating sites will remain unaware of the study group outcomes until the database is locked.

This has been specified in the paper in the “randomization” paragraph (page 12).

’SStatistical Analysis’ section, mentions ‘Security will be analysed’, this should be changed to ‘safety’. You refer here to SAEs, but have not mentioned collection of SAEs or reporting in the protocol. Please add this additional safety information including details of the study sponsor, as part of the ‘ethical considerations’ or ‘data safety and monitoring’ section.

The term “security” has been replaced by “safety”.

Regarding the serious adverse events, we thank the reviewer for pointing out this omission. All adverse events will be recorded in the case report form (CRF) on the specific pages reserved to this end. A simplified procedure will be used for “foreseeable” adverse events (hemodynamic instability, rhythm disturbances, electrolyte or acid-base imbalance, bleeding events related to hemodialysis catheters or anticoagulants). Adverse events will be considered as serious if they cause death, are life-threatening, cause hospitalization (or prolongation of initial hospitalization), cause disability or permanent damage or a congenital anomaly or birth defect.

Investigators must report any serious adverse event to the sponsor promptly by email or telephone, followed by a written report within 48 hours.

These details have been added in the revised paper, in the “data collection” section (top of page 14). The details of the study sponsor have been added at the very beginning of the “methods” section (first paragraph) for clarity.

3. Is the planned statistical analysis appropriate?

Yes, the statistical analysis section is appropriate for the data and will answer the research questions.

Thank you.

4. Is the writing acceptable?

This is a well written protocol which is clear and concise. References are correctly cited and listed in the style requested for Trials.
Thank you.

The abstract contains all pertinent information and adheres to CONSORT guidance, but abbreviations are used which are not allowed in the Trials instructions to authors. The abbreviations have been spelled out in full in the abstract, as requested.

There is a good discussion of the strengths and weaknesses of the study, including potential challenges of implementation.

Thank you.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. Reference to RIFLE classification should be clear the first time it is quoted

2. Further detail on the consent procedure required - add to the ‘Trial Protocol’ section before randomization, and/or a full explanation should be provided as part of the ‘ethical considerations’.

3. Study flow diagram should be added

4. Add detail on choice of effect size used for the sample size calculation, and move section to ‘Trial Protocol’

5. Add further detail on allocation ratio for randomization, and blinding

6. Add further information on safety reporting and study sponsorship

All these points have been addressed – see replies to each point above.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

7. Change word ‘security’ to ‘safety’ in statistical analysis section

This has been corrected.

Editorial requests:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?____________: study protocol for a randomized controlled trial.? The title has been amended accordingly.

2. Please include the date of registration with your trial registration number at the end of your Abstract.
The date of first release of the ClinicalTrials.gov record for this study has been added after the trial registration number at the end of the abstract.

3. Please include the reference numbers given with ethical approval with your ethics statement in the Methods section.

The reference number of the ethics committee approval has been added in the relevant section.

4. Please include a list of abbreviations used and their meanings, after your Trial Status.

A list of abbreviations used in the paper has been added after the “Trial Status”.