Reviewer’s report

Title: A randomized controlled trial of the 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)

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Reviewer: Judith Cohen

Reviewer’s report:

Study protocol – Review for publication in Trials
A randomized controlled trial of the 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)

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Trials (Submitted: 2014-01-27)

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.

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.
- 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’.

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

- 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. 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?

- 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.

- ‘Statistical 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.

3. Is the planned statistical analysis appropriate?

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

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. 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.

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

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'