Title: Intravenous iron isomaltoside 1000 administered by high-single dose infusions or standard medical care for the treatment of fatigue in women after postpartum haemorrhage: study protocol for a randomised controlled trial

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Author's response to reviews: see over
Editorial requests:

1. Please include the date your study was registered with the trial registration number at the end of the Abstract.
   CH: The data of registration with clinicaltrial.gov has been added

2. Please state clearly whether or not you have funding in the Acknowledgements section. If there is no funding, please state this.
   CH: We have added the information on funding to the Acknowledgement section.

Reviewer's report

**Title:** Intravenous iron isomaltoside 1000 administered by high single infusions or standard medical care in treatment of women after postpartum haemorrhage: study protocol for a randomised controlled trial

**Version:** 1  **Date:** 13 September 2014

**Reviewer:** Rohan D'Souza

**Reviewer's report:**
This is a well-designed trial on a clinically important topic. The protocol provides a clear rationale for the conduct of this trial, its open label design, and the choice of a 'standard individualized regimen' over a 'fixed regimen' in the comparator arm.

**Major compulsory revisions:**

**TITLE:**
Does not explicitly specify what is being treated. Suggested change: “… for the treatment of fatigue (symptoms) in women after PPH” rather than “…treatment of women after PPH”
CH: We agree and have changed to the suggested.

**KEYWORDS:**
Consider “iron deficiency” instead of “iron deficiency anaemia” in keeping with the trial’s objectives
CH: We agree and have changed to the suggested.

**BACKGROUND:**
First paragraph:
   CH: The references have been updated to the suggested.

2. Rationale for choosing a cut-off level of 700ml requires further clarification
We have added further clarification to the background section (postpartum iron deficiency and anaemia).

Intravenous iron (5th paragraph): The rationale for choosing iron isomaltoside 1000 is briefly described. However, given that “no difference in safety profiles of IV iron preparations has been established”, the choice of this agent over other IV iron preparations requires clarification.

CH: We have elaborated on the choice of iron isomaltoside 1000.

METHODS AND DESIGN:
Inclusion criteria: It is implied that all women, regardless of mode of delivery will be included in the trial, although this has not been explicitly mentioned anywhere in the protocol. I suggest mentioning this explicitly at least under ‘inclusion criteria’.

CH: We agree, and have added this under inclusion criteria.

Intervention (2nd paragraph): Choosing a fixed dose rather than a dose calculated based on haematological markers and/or body weight may be appropriate, but the rationale needs further clarification.

CH: We find the fixed dosage most appropriately in this population, and have further clarified the rationale.

Outcome and safety measures: Details need to be provided on what constitutes “other relevant iron and RBC related biochemical parameters” and “biochemical safety parameters”.

CH: We agree, and have provided details on the specific parameters.

Questionnaires:
1. Although mentioned in the Discussion, whether or not the PPQ instrument has been validated in this population must be specified here.

CH: We have added the information to this section.

2. Those routinely caring for postpartum patients would be able to deduce the rationale for the use of the EPDS but this is not immediately obvious to the reader and merits comment.

CH: We agree, and have added more details about the EPDS.

Number of participants: Whether the “10% difference” is based on consensus, expert opinion or published data must be specified.

CH: We have elaborated in this section on the basis of the “10% difference”.

Statistical analysis:
1. The analysis is presumably going to be on an ‘intent-to-treat’ basis. This needs to be explicitly mentioned.

CH: The primary analysis population is the full analysis set (FAS). The sentence has been edited to clarify this. The reason for choosing FAS (all rand. subjects who received the study drug, and have at least one postpartum baseline physical fatigue score) instead of ITT is due to the design of the study. The study drug is given in one total dose, so
potentiale randomized participants who withdraw consent before or during treatment will have no outcome measures after baseline and are therefore not included in the analysis.

2. The statistical methods seem reasonable, although I would defer a detailed review of this section to a statistical expert.

Consent and ethical considerations: Is there a Data Safety Monitoring Board? If not, the decision not to have a DSMB needs to be explicitly justified.

**CH:** There is no DSMB. This trial is a phase 4 study. The safety profile of the study drug is well known and the drug has the approval from the appropriate regulatory agencies.

Discussion: Fatigue as a subjective endpoint merits a more detailed discussion – although subjective, it is still a very important clinical endpoint and one of the few clinical endpoints to consistently be shown to be affected in IDA and ID. However, fatigue in the immediate and later postpartum period is highly dependent on various attributes including the mode and outcome of delivery, the duration of labour, medical co-morbidities, the health of the infant and a host of social and environmental factors, and this inherent weakness must be highlighted.

**CH:** We agree and have edited the section using your comments for the discussion.

Minor essential revisions (not for publication):

**CH:** Thank you for the thorough spelling and typographical review. We have corrected the manuscript accordingly.

Although the trial has been commenced, given that this is a protocol, consider uniform use of future tense throughout as indicated below. Also, consider the following spelling/typographical changes:

**Abstract** – Methods (penultimate paragraph)
Consider changing "...with regards to..." to "...with regard to..."

**Abstract** – Methods (last paragraph)
Consider changing "proclaiming:" to "claiming"

**Background** – paragraph 1
Consider changing "...clinical relevant..." to "...clinically relevant..."

**Intravenous iron** – third paragraph
Consider changing "immunologenic" to "immunogenic"

**Previous studies and current guidelines** (4th paragraph)
Consider changing "...down to..." to "...as low as..." and "...balanced to..." to "...balanced against..."

**Study design**
Consider changing "...company sponsor..." to "...company-sponsored..."
Inclusion criteria
Consider changing "2) has either" to "2) have either"

Exclusion criteria
Consider changing "…not able to…" to "…inability to…"

Randomisation
Consider changing "Are/is" to "Will be"

Outcomes and safety measures (2nd paragraph)
Consider changing "…secondary efficacy outcomes are…” to "…secondary efficacy outcomes include…” and "… breastfeeding, transfusion…” to "… breastfeeding and transfusion…”

Number of participants
Consider changing "…clinical relevant…” to "…clinically relevant…”

Statistical methods and analysis
Consider changing "randomised" to "randomised" and "Fatigue score is calculated" to "Fatigue score will be calculated"

Consent and ethical considerations
Consider changing "All women planned …" to "All women planning to …" and "In relation to one of…” to "At (or during) one of…”

Consider changing "Is/ complies" to "Will be/ will comply"

Discussion (2nd paragraph)
Consider changing "The pregnant women usually take… and find…suitable for her" to "A pregnant woman usually takes… and finds…suitable for her."

Also, Consider changing "Thus, as comparator" to "Thus, as a comparator,"

Discussion (3rd paragraph)
Consider changing "…detail information…” to "…detailed information…”

Discussion (4th paragraph)
Consider changing "…tablets colours the stool…” to "…tablets colour the stools…”

Consider changing "A double-blinded design is assessed to be not valid and will not contribute with scientific value" to "A double-blinded design was assessed to be unfeasible and unable to contribute additional scientific merit."

Discussion (last paragraph)
Consider changing "There is however no validated questionnaires" to "There are…”
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

CH: This revised version of the manuscript have been reviewed and edited by a native English proofreader

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests