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"

KEYWORDS:
Consider “iron deficiency” instead of “iron deficiency anaemia” in keeping with the trial’s objectives

BACKGROUND:
First paragraph:
2. Rationale for choosing a cut-off level of 700ml requires further clarification

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.

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’.

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.

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

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

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

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

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.

Minor essential revisions (not for publication):

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

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