Reviewer's report

Title: Statistical analysis plan for erythropoietin in traumatic brain injury (EPO-TBI): a randomised controlled trial

Version: 2

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Reviewer: Andrew Maas

Reviewer's report:

This manuscript describes in detail the statistical analysis plan for the ongoing randomized controlled trial on erythropoietin in TBI (EPO-TBI). As the authors state it is highly relevant to describe the statistical analysis plan prior to lock of the database and initiation of analysis. The authors are to be congratulated on their attempts for complete transparency in the reporting of this important trial. I have a number of relatively minor issues:

1. In various sections of the manuscript the authors use the term 'phase III superiority trial'. This is for example mentioned in line 2 of the result section of the abstract, twice in the introduction and again in the methods section. I am not so familiar with the term superiority trial and if this is a generally accepted phrase in the domain of clinical trials. If not, the risk may be that some reader misinterpret it as if EPO-TBI as a study is superior in quality – which it may be but it is not up to the authors to state this. In understand that this is definitely not the intent of the authors but nevertheless the risk exists that some readers may interpret it as such. My suggestion would be to delete the word superiority.

2. The plan sample size is based on a power calculation to detect a reduction in unfavorable outcome from 50 to 36%. It would appear that the sample size of 606 patients may be rather low to achieve such an absolute reduction but this may be possible with the use of covariate adjustment. I further note that trial sample size was calculated for the primary outcome using an estimate base line of 50% proportion of unfavorable neurological outcome. The assumption of a 50% proportion of unfavorable neurological outcome in power calculations in fact relates to a 50% change of unfavorable outcome in every patients. This, obviously, is never the case and some patients will have higher and others a lower risk of unfavorable neurological outcome. The assumption underpinning the power calculation of a 50% proportion of unfavorable outcome is therefore open to criticism.

3. In line 7 of page 7 the authors refer to a manuscript by Nicohl et al in preparation, describing the trial protocol in detail. Is this indeed in preparation or is it perhaps submitted?

4. Page 9: here it is stated that ‘a nominated statistician who will supervise data extraction from the database for interim and final analyses’. The previous sentence that this individual unblinded. I fail to understand why the statistician responsible for interim and final analysis should be unblinded. The statistician
should be aware of group A and group B but I would prefer to see the statistician blinded as to treatment allocation.

5. On page 11 under ‘Secondary outcomes, and pre-specified covariates’ the authors state that they will adjust for pre-specified base line covariates as well as ‘any covariate exhibiting substantial imbalance between randomisation arms’. I recognize that there may be various opinions here but submit that preferably adjustment should only be performed for pre-specified base line covariates. Please explain and motivate why you also include any covariate exhibiting substantial imbalance; I would also suggest defining what is meant by ‘substantial imbalance’.

6. On page 14 the authors state that the two interim analysis are expected to have a negligible effect on expenditure of error. And that therefore the level of significance will not be adjusted for multiplicity. To me as clinician this seems a bit strange, but I defer opinion to my statistical colleagues.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: 

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