Author's response to reviews

Title: Statistical analysis plan for erythropoietin in traumatic brain injury (EPO-TBI): a randomised controlled trial of erythropoietin versus placebo in moderate and severe traumatic brain injury

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Version: 3
Date: 17 November 2014

Author’s response to reviews: see over
Dear Editors

**MS: 1675903727143178 - Statistical analysis plan for erythropoietin in traumatic brain injury (EPO-TBI): a randomised controlled trial**

Thank you for the insightful peer-review and editorial comments recently communicated to us. Please find attached our revised manuscript, accompanied by a point-by-point list of replies to all questions.

The revised manuscript is named:

“Trials MS_1675903727143178 EPO-TBI_statistical analysis plan_R1_15Nov2014_final.docx”

We hope that our answers and revisions are satisfactory, and look forward to your next communication.
In conclusion we are delighted to advise that the EPO-TBI trial reached its target recruitment of 606 subjects on 1st November 2014. The revised manuscript has been adjusted in several places to report that fact, with the final collection of all 6-month outcome data now due by May 2015. Soon after that time, this statistical analysis plan will be implemented.

Kind regards

Lorraine Little, on behalf of the EPO-TBI Investigators, and the ANZICS Clinical Trials Group

**Referee 1:**

Comments and questions as contained in http://www.trialsjournal.com/imedia/2154918214698030_comment.pdf are addressed below individually.

**Q1** ‘phase III superiority trial’

The term superiority is used in accord with an international statistical guideline for clinical trials which is listed as reference number 9 in this manuscript. Specifically, the term superiority is defined by paragraph 3.3.1 (“Trials to Show Superiority”) in that document titled “International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) harmonised tripartite guideline E9 - statistical principles for clinical trials”. That guide states “…efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial... This type of trial is referred to as a ‘superiority’ trial...”

No change is proposed to the manuscript on this point.
Q2 Reviewer’s questions about sample size, power and binary compared to ordinal analyses

The authors believe that the current combination of a primary unadjusted binary analysis with secondary adjusted binary logistic and ordinal regression analyses comprise an acceptable plan for the assessment of the data in this traumatic brain injury randomised controlled trial.

Q2 (a) 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.

No change is proposed to the manuscript on this point.

The primary outcome of this study is defined from a traditional mid-point dichotomization of the eight level ordinal Extended Glasgow Outcome Scale (GOSE).

From this, the proportion of patients with unfavourable neurological outcomes at six months will comprise those patients with severe disability (defined as a GOSE 2-4) or death (GOSE 1), with analysis according to treatment using an uncorrected Chi-square test. This midpoint dichotomization of the GOSE has been widely used in other traumatic brain injury studies.

The sample size determined for EPO-TBI, which was necessarily based on this primary binary outcome, had two important aims. These were to have adequate power simultaneously:

1. to find an important difference in brain functional outcome if one existed with EPO therapy, and
2. to detect a clinically relevant increase in the proportion of patients with deep venous thrombosis (DVT) should there be evidence of that important potential toxicity accompanying administered erythropoietin in this trial.

As designed, the sample size of 606 subjects, randomised 1:1 between EPO and control arms, incorporated an approximate 5% sample size inflation for losses to followup, making the trial aim to recruit at least 574 evaluable subjects (287 in each of two treatment arms).

Using conventional calculations, a study of 574 fully evaluable subjects would deliver slightly over 90% power to detect a 14% absolute risk reduction (50% vs. 36%) [a 28% relative risk reduction], and slightly over 80% power to detect a 24% relative risk reduction (50% vs. 38%) in 6 month unfavourable neurological outcomes (at a two sided alpha of 0.05).

Importantly, that trial size will also deliver slightly greater than 80% power to detect a 9% absolute risk increase in the proportion of actively treated subjects with proximal DVTs from an assumed 18% occurrence rate in control subjects (50% relative risk increase), at a one sided alpha of 0.05. Such one-sided efficacy calculations assume a “non-superiority in the proportion of DVT” design.

Q2 (b) 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.

No change is proposed to the manuscript on this point. We believe that the combination of a primary binary analysis with secondary adjusted analyses and ordinal regression form an acceptable plan for these traumatic brain injury data.
Our expert reviewer, Professor Maas, is completely correct that there will very likely be heterogeneity between trial patients with respect to their risk of an unfavourable neurological outcome. How best to analyses traumatic brain injury trial outcomes has been the subject of several recent publications, including from Professor Maas and colleagues who reported (in his manuscript which is listed as our reference number 17) an added value of ordinal analysis over simple binary analysis in traumatic brain injury.

Professor Maas may be noting that the relative efficiency of our simple $2 \times 2$ binary Chi-square analysis using the midpoint dichotomized GOSE outcome category may be less than that of an ordinal logistic approach using the proportional odds model in the eight level GOSE outcome scale. However, use of an ordinal logistic regression analysis rather than a simple binary model relies on more statistical assumptions and may deliver less useful information gains in practice. With head injury outcome data, the power gain (improved asymptotic efficiency) derived from using a cumulative odds model may be relatively modest over a simple binary analysis in the very common setting of asymmetrically distributed GOSE outcome categories (Ananth CV, Kleinbaum DG. 1997. Regression models for ordinal responses: a review of methods and applications. Int.J Epidemiol. 26:1323-33 and Armstrong BG, Sloan M. 1989. Ordinal regression models for epidemiologic data. Am J Epidemiol 129:191-204). Importantly, recent statistical simulations (Price M, V. Hertzberg, and D. W. Wright. Does the sliding dichotomy result in higher powered clinical trials for stroke and traumatic brain injury research? Clin.Trials 10 (6):924-934, 2013) based on traumatic brain injury data do not confirm an advantage for the formerly promoted “sliding dichotomy” model over binary analyses.
Regardless, the EPO-TBI trial will take advantage of any greater power afforded by other models of analysis through the specification of important secondary outcomes of the EPO-TBI trial, including covariate adjusted binary logistic models and a proportional odds cumulative logit model applied to the eight-level vector of six month GOSE rather than its midpoint dichotomization. Under the assumption of proportional odds, the anticipated effect of achieving a reference improvement with EPO treatment is a systematic shift of patients into better categories of outcome.

Q3 In line 7 of page 7 the authors refer to a manuscript by Nichol et al in preparation, describing the trial protocol in detail. Is this indeed in preparation or is it perhaps submitted?

This sentence has been changed to use the word “submitted” rather than “in preparation”:

“…a forthcoming manuscript (Nichol A et al, submitted)…”

Q4 Page 9: Blinding of statistician with respect to treatment allocation during trial analysis

Professor Maas is correct to advise against unblinding the statistician who will implement this statistical analysis plan once the final trial data set with 6-month outcomes for all evaluable patients is cleaned and locked.

There will be two statisticians involved with the EPO-TBI trial. As stated earlier on page 9:

“…a nominated statistician … will supervise data extraction from the database for interim and final analyses…“.
This first statistician is familiar with the EPO-TBI trial aims and data fields, so his work will be necessary to achieve an error-free final data set ready for analysis.

To clarify the pivotal role of a second blinded statistician, a later sentence extending over pages 9 + 10 has been modified addition underlined, as follows:

“...When final database entries have been made and final queries have been resolved, the EPO-TBI research database will be locked. Application of this trial statistical analysis plan to the computation of treatment effect estimates will then proceed with a second, independent statistician using a blinded binary indicator of treatment to generate primary and secondary effect estimates. These estimates will be incorporated in the trial final report by the trial’s writing committee while unaware of the treatment code.

Q5 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’.

No change is proposed to the manuscript on this point.

In the EPO-TBI trial, an unadjusted analysis has been selected as the one for primary attention, with various adjusted analyses being supportive. The large paragraph titled “Secondary outcomes, and pre-specified covariates” extending from Page 11 to Page 13 described in detail the secondary analyses that will be performed to assess the
sensitivity of the primary conclusion to adjustment for those covariates and factors expected to have an important influence on the primary variable.

A randomised trial of 606 subjects is substantial in size, and thus will likely deliver good balance of all relevant factors between treatment and control groups. However, as noted by a research guideline published in 2013 (European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on adjustment for baseline covariates. EMA/295050/2013 www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC_500144946.pdf), it remains possible that a baseline imbalance may be observed post hoc. Provided the randomization process was not compromised, any observed imbalance must always be a random phenomenon.

As recommended by the European Medicines Agency 2013 guideline, if such unexpected baseline imbalance is observed in the EPO-TBI trial for a possible risk factor, sensitivity analyses including the baseline measure as a covariate will be performed in order to assess the robustness of the primary unadjusted analysis.

A sentence on page 11 in the EPO-TBI manuscript will be modified to make this intention clear, with the addition of a citation to the European Medicines Agency guideline: “…Sensitivity analyses of the primary and secondary outcomes will be performed using logistic regression adjusting for pre-specified baseline covariates as well as any covariate exhibiting substantial imbalance between randomisation arms, as recommended [14]…”

Q6(a) On page 14 the authors state that the two interim analysis are expected to have a negligible effect on expenditure of error
The EPO-TBI statistical analysis plan notes that a group sequential statistical approach was used to perform two equally-spaced interim analyses (at 33% and 66% of total recruitment) to assess the trial primary outcome using the Haybittle-Peto criterion (|Zk| ≥ 3) for early stopping. This process is explained in much more detail in the standard textbook reference quoted (Jennison C, Turnbull BW: Group sequential methods with applications to clinical trials. Boca Raton, Florida: Chapman & Hall/CRC; 2000).

Implementation of the specified Haybittle-Peto criterion for these two interim analyses caused only a small expenditure of error, with the final critical value |Z3| ≥ 1.975 being equivalent to a P value 0.048, rather than the familiar P value of 0.05 associated with a single analysis at |Z| ≥ 1.960).

Because this difference in threshold for statistical inference at the conclusion of the trial (P = 0.048 versus P = 0.05) was regarded by the trial design committee as negligible for a trial of 606 subjects, the final analyses at full recruitment will be conducted with the more familiar Type I error alpha equal to 0.05.

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**Q6(b)** And that therefore the level of significance will not be adjusted for multiplicity.

No change is proposed to the manuscript on this point.

As correctly noted by Professor Maas, multiple analyses will be performed of the EPO-TBI data assessing various outcomes, both unadjusted and adjusted.

As recommended in our manuscript’s reference number 9 (E9; statistical principles for clinical trials; paragraph 5.6 Adjustment of Significance and Confidence Levels) the EPO-TBI trial reduces the risk of multiplicity by clearly specifying only one primary trial outcome, supplemented by other secondary sensitivity analyses.