Reviewer's report

Title: Transfusion Indication Threshold Reduction (TITRe2) randomised controlled trial in cardiac surgery: statistical analysis plan

Version: 1

Date: 12 September 2014

Reviewer: Catherine D'Este

Reviewer's report:

1. This paper presents a comprehensive plan for analysis of the Transfusion Indication Threshold Reduction (TITRe2) RCT. Although the paper presents a statistical analysis it could still be helpful to include a bit more detail on some aspects of the study protocol.

Major Compulsory Revisions

2. The paper should outline any changes to the basic analysis plan since the trial protocol was registered (in addition to the sensitivity analyses which were not specified in the original protocol).

3. A summary of the sample size justification and the power for subgroup analyses should be included.

4. The terminology / explanation around withdrawals is a little confusing. Different types of withdrawals are defined, but then the clinician decision to discontinue treatment is described as not being a withdrawal.

5. While the flowchart indicates that EQ5D will be obtained at 6 weeks and three months, it is unclear if any other measures will be obtained at these follow-up times. The 6 week data collection wave is not specified in the flowchart.

6. When dealing with potential outliers, what will be the process / justification for excluding observations? There will need to be a very strong justification for excluding any observations from the main analyses – this will violate intention-to-treat analyses; if necessary sensitivity analyses could potentially exclude unusual observations.

7. Table 4 specified that marginal mean imputation will be undertaken if between 5% and 15% of observations have missing outcome data. This is not an advisable / appropriate option for imputation of missing data as it is not generally valid under the Missing at Random (MAR) assumption and will underestimate the variance of the treatment effect.

Minor Essential Revisions

8. It would have been helpful for the Introduction to begin with a brief background / rationale for the study.

9. Details on the number of centres and number of different types of operation should be included. Knowing the number of centres and the number of patients per centre would be beneficial when considering the utility of the sensitivity
analysis estimating treatment effects by site.
10. Is Study Objective a) to estimate the relative or absolute risk of infection?
11. Modified intention-to-treat analyses will be performed – what is the “modification”?
12. What variance / covariance structures will be considered? Ideally only a limited set of structures will be considered and there should be a rationale for these.
13. In Table 2, it is not clear whether the primary outcome includes all five outcomes listed, or just with first two, with use of activated factor seven, beriplex and significant pulmonary morbidity considered as separate outcomes. Similarly, do the measures listed under continuous outcomes represent one or multiple separate outcomes?
14. The flow chart would benefit from inclusion of a definition of the study population.

Typographical errors:
15. TITRe2 should be written in full the first time referenced.
16. Introduction, paragraph 2, line 4, analysis is misspelt.
17. Patient population, line 3, “that are not eligible” should read “that they are not eligible”.
18. Sensitivity analyses, point 3, line 1: delete the comma after “by”
19. Page 10, line 2: delete the comma after “recruited”
20. Page 10, Safety data, line 4: there is a unnecessary symbol after “hospitalisation”
21. My version of the document has some missing symbols (this could just be a function of the formatting of my printer):
22. Page 9, line 1: > missing for > 75
23. Page 9, line 4: < missing for eGFR < 60ml/min
24. Page 9, sensitivity analyses, point 4, line 2: the sign missing before 26.5umol/l and before 150%.
25. Page 9, last dot point, fourth last line, sensitivity analysis b): should “including patients” read “excluding patients”?
26. Page 11, middle paragraph, line 4: “multivariate” should be “multivariable”.

Discretionary revisions
27. What analysis was requested by the Data Monitoring and Safety Committee?
28. The flow chart indicates that EQ5D data were obtained for non-randomised patients prior to surgery and at 3 months. Is there any plan for analyses of these data?
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:

I declare that I have no competing interests