Author's response to reviews

Title: Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness

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Version: 2
Date: 28 October 2014

Author's response to reviews: see over
Response to reviewer’s comments

Title: Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness

Version 1; Date: 22 September 2014

Reviewer 1: Walter Dzik

Major compulsory revisions:

1. Need to emphasize more strongly the fatal consequences of delay in transfusion.

The single most striking finding of this paper—both clinically and statistically—is the following: delay in blood transfusion, even for a few hours, for children who present with severe anemia is a fatal delay. The authors data demonstrate that, among children with severe anemia, those who receive transfusion > 8 hours after presentation have a 12-fold higher death rate than those transfused more promptly. This is the most important “take away” message because it means there is strong justification for having all pediatric acute care centers stocked at all times with a supply of group O “emergency release” blood available. The actual data from the paper are:

…..Among those with Hb < 5 g/dL:
Tx < 8 hours Tx > 8 hours
Dead 39 54
Alive 860 49

This corresponds to unbelievably high chi-square of 250 with a p<< 0.00001.

Stated another way, only 4% of children with severe anemia who were transfused within 8 hours died. This value (4%) is little different from the “background” fatality rate among the entire group. In striking contrast, 52% of children with severe anemia who had delays in transfusion died.

I would recommend that the authors make this very important part of their analysis a centerpiece statement in their Results, Conclusion, and Discussion because this data has direct policy implications for blood availability and childhood mortality in sub-Saharan Africa.

While the importance of prompt transfusion is clearly of greatest value in the severely anemic subset of children, it is notable that even in the overall dataset, there remains a fatal price for delay, as shown by the data:

All transfused patients:
Transfused < 8 hours > 8 hours
Dead 57 95
Alive 1061 1133
P< 0.0116

RESPONSE

We entirely agree with the reviewer that any delay in transfusion is likely to be deleterious, and 52% (54/103) of those children with Hb<5g/dl who were not transfused had died by 8 hours (see Table 6). However, of the 54 children that died without a transfusion, 90% died within 2.5 hours of randomisation and 100% within 5 hours. This is confounding the comparison in the first of the reviewer’s 2 x 2 tables, as these children would have been transfused before 8 hours had they lived long enough. To help clarify this we have edited the text in Table 6 and have added a footnote to reflect when the death occurred.
The same is true of the second of the reviewer’s 2 x 2 tables: the high mortality in the second column of the 2 x 2 table is confounded by the fact that these children did not live long enough to receive a transfusion. (Please also note that we cannot see where the numbers 95 and 1133 in the reviewer’s 2 x 2 table have come from!).

2. Need to report the interaction effect of bolus volume loading on top of transfusion.

A concern in this data (and in the FEAST trial) is that it seems possible that some children presented with severe anemia (Hb < 5) without hypovolemia, and that these children might have been randomized to receive 40 mL/kg of 5% albumin and THEN also transfused with an additional 20 mL/kg of whole blood. Since both 5% albumin and whole blood are fluids confined to the intravascular space, these children may have received 60 mL/kg of intravascular volume in short order. This represents a volume nearly equal to the child’s entire blood volume, or ...a sudden doubling of intravascular volume. The question is whether or not excessive fluid overload may have contributed to mortality. Although the authors present data (in Figure 2) that bolus vs non-bolus did not vary when stratified by presenting Hb, Readers would like to know whether bolus therapy on top of transfusion therapy was deleterious. So, please present an analysis of the following:

Among the subset of transfused individuals.....
Bolus arm No bolus arm
Dead a b
Alive c d
And

Among the subset of transfused children presenting with Hb < 5 who also received transfusion...
40 mL/kg 5% albumin No bolus arm
Dead a b
Alive c d

RESPONSE
We agree with the reviewer that this question is of interest to readers, but feel it is beyond the scope of this paper. This is because increased fluid (both including and excluding blood) is subject to time-dependent confounding, since it is associated with both the severity of the child’s illness and their survival time. However, analyses examining a dose-response effect of the bolus and blood together on mortality are on-going, and will be published in a separate paper.

Near the end of the trial there was a protocol amendment to increase the initial bolus to 40mls/kg which can provide some information to answer the reviewer’s question. A subgroup analysis showed that there was no difference between children enrolled before the amendment (who got an initial bolus of 20mls/kg) and those enrolled after the amendment (who got an initial bolus of 40mls/kg)(presented in the original NEJM paper).

If we restrict this analysis to those who had hb<5g/dl at baseline we find the risk ratio for mortality comparing comparing albumin to no bolus control was 1.79 (95% CI 1.12-2.85) before the amendment and 1.77 (0.64-4.9) after the amendment (heterogeneity p-value 0.98) showing no evidence for a difference between these groups. All children enrolled into the FEAST trial had clinical evidence of impaired peripheral perfusion (based on the standard clinical assessment of shock), since this was one of the primary inclusion criteria.
3. Factors contributing to a fatal outcome:
In addition, it would be very instructive to do a simple logistic regression analysis restricted to the TRANSFUSED children using death as an outcome to determine the factors significantly contributing to a fatal outcome. Input variables would certainly need to include:
* presenting Hb
* <8 hours vs >8 hours before transfusion
* 5% albumin, saline, no bolus
* presenting lactate <5 or >5
* received whole blood or received packed cells
* other data as you will see fit.
This analysis would help us to understand which co-factors were most significantly related to adverse outcomes among the transfused cohort.
(You might consider the same approach restricted to the subset of children who presented with Hb <5 since most of the death is clustered in this category.)

RESPONSE
We have considered the reviewer’s request for information regarding mortality in those transfused. We have created a logistic regression within those who were transfused by 8 hours, looking forward at mortality after 8 hours and before 48 hours, in order to minimise confounding by time.

Table: Odds of mortality between 8-48 hours for those transfused before 8 hours

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>Wald p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most recent haemoglobin*</td>
<td>1.02 (0.87-1.21)</td>
<td>0.76</td>
</tr>
<tr>
<td>Most recent lactate*</td>
<td>1.27 (1.19-1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid bolus</td>
<td>1.86 (0.90-3.84)</td>
<td>0.09</td>
</tr>
<tr>
<td>Packed or whole blood</td>
<td>0.8 (0.32-1.98)</td>
<td>0.63</td>
</tr>
<tr>
<td>Time to transfusion from randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-&lt;4 hrs</td>
<td>1.63 (0.74-3.58)</td>
<td>0.23</td>
</tr>
<tr>
<td>4-&lt;6 hrs</td>
<td>0.61 (0.14 – 2.58)</td>
<td>0.53</td>
</tr>
<tr>
<td>6-&lt;8 hrs</td>
<td>0.70 (0.14-3.54)</td>
<td>0.67</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0.72 (0.37-1.39)</td>
<td>0.32</td>
</tr>
<tr>
<td>Conscious level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostrate</td>
<td>1.11 (0.37-3.34)</td>
<td>0.85</td>
</tr>
<tr>
<td>Coma</td>
<td>6.5 (2.04-20.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*This is the 8 hour measurement, if available.; if the 8-hour measurement was not available it was replaced by the admission measurement (n=38 for lactate, n=54 for haemoglobin)

We do not plan to add this to the manuscript as our analyses are focussed on transfusion practises within the countries and sites participating in the FEAST trial. The questions that the reviewer is asking (predictors of mortality in transfused children) are not clearly answerable in this cohort, and would be better addressed in cohorts where every child is transfused as standard, rather than in one that may be affected by selection bias (since transfusion was not a unit of randomisation). The trial cohort includes a heterogeneous group of very high-risk children presenting with impaired perfusion due to many common infectious aetiologies at baseline, and 183/315 deaths occurred prior to 8 hours, so could not be included in the analysis above.

4. Need to de-emphasize certain features of the current conclusions:
The current manuscript should undertake, in this reviewer’s opinion, some adjustments to the stated conclusions of the paper.

Looking at the abstract, one reads:

a) “Severe anemia is a leading cause of death in children presenting to hospitals in East Africa with a febrile illness.” However, the data presented in this paper do NOT tabulate all the causes of death and so one cannot conclude (from the data given) that severe anemia is a leading cause. You CAN say: “Death occurs in 13% of children who present with severe anemia and a febrile illness in East Africa.”

**RESPONSE**
We have adjusted the phrasing of the abstract accordingly.

b) “The high rates of re-transfusion...”.
Actually, the rates of re-transfusion are low. In the Kenya data, 98% of children did NOT need re-transfusion. Overall, more than 90% received only one transfusion. I suspect that with a good look at the data you will be able to conclude: “Overall, the great majority of children required one transfusion. However, the lower the presenting hemoglobin concentration, the more likely that a child received a second transfusion. Re-transfusion was given to x% of children presenting with a hemoglobin < 5 g/dL.”

**RESPONSE**
We disagree with this statement. 1387/3082 (45%) of all children in this study were transfused (Table 3). Of those transfused, 317/1387 (23%) were re-transfused. Among severely anaemic children, 94% (933/1002) were transfused, and 29% (275/933) were re-transfused.

c) The conclusion about “under treatment of a significant proportion of anemic children” is not supported by the overall data. Indeed, it is a small minority. Better just to report the number and not an adjective.

**RESPONSE**
We disagree with this statement (see 4b, above): 23% of anaemic children in this study required re-transfusion.

d) “A clinical trial to evaluate the impact of larger volume...” This statement should be removed as a conclusion from the abstract and from the final paragraph. It is not a “conclusion” of the presented data. The manuscript should stand on its own as an analysis of what you found and should not be presented as a “justification” for a planned study. The announcement of the study can certainly be presented in the Discussion, but it simply isn’t an analytic conclusion. These same concerns (regarding conclusions) arise at the end of the manuscript.

**RESPONSE**
We consider that the data presented in this study provide powerful justification for a clinical trial evaluating the impact of a larger volume of transfused blood. This is an important conclusion, which should be reflected in both the Discussion and the Abstract. We have made a minor adjustment to the phrasing of the final sentence of the abstract.

**Minor essential revisions:**
5) Results, end of prevalence section: The authors report that the prevalence of severe anemia was lowest in Kilifi (13%) and highest in eastern Uganda (39-43%). A few sentences later, they report that the proportion of children receiving 2 or more transfusions was lowest in Kilifi (<5%) and highest in eastern Uganda (23-38%). I expect you will find that these two observations are tightly related. When a child presents with a Hb= 2 g/dL and is treated properly, his post-transfusion Hb is still likely to be low and so a second transfusion is likely to occur. When a child presents with an Hb=4.5 g/dL and is treated properly, a second transfusion is not likely to be needed. This is simply a matter of the “dose-response balance sheet of red cell mass”. So, while you are quite correct to acknowledge that the higher rate of re-transfusion in eastern Uganda (and esp at Mulago) might be (in part) related to greater access to transfusion (your comment in the Discussion), you are likely to find a statistically significant association between presenting Hb and need for re-transfusion. I recommend you undertake demonstrating this association because it would clarify the importance of this “driver” for re-transfusion for the Reader.

RESPONSE
Thank you for this observation. We have now provided an analysis of clinical predictors for re-transfusion. Admission haemoglobin level was strongly predictive of re-transfusion (Table 5). Re-transfusion was, however, twice as likely at Mulago hospital compared to the other sites, even when controlling for admission haemoglobin level, showing that site-specific practises also have a large impact on re-transfusion rates.

6) Results: Number and Type of Transfusions: Given the high rate of death that was attributed by the independent adjudicators to “cardiovascular causes” and the very low rate of treatment with furosemide (only 5 children out of >1000), do you think that there may have been tremendous “under-recognition” of cardiac strain in this cohort? I think so. While you present the information (Results) that only 5 children received furosemide, you may want to comment on this in light of the high rate of cardiovascular death.

RESPONSE
Thank you for pointing this out. We have now added a comment to the paragraph on outcome of transfusion. An independent review committee, who were blind to randomised arm, considered the majority of deaths in the bolus arm to be cardiogenic shock, and indicative of myocardial dysfunction rather than biventricular failure (reference 41). Pulmonary oedema was a specific adverse endpoint in FEAST, and clinicians had to report on its presence or absence at every clinical review. All clinicians received pre and peri-trial training on adverse endpoints, and any case with suspected pulmonary oedema required reporting to the Endpoint Review Committee (ERC) and Data Management Committee. Most events were adjudicated by the ERC (blind to randomised arm) as being unlikely to have been related to the trial intervention.

7) Discussion, paragraph #3: “…though more recent work suggests that metabolic acidosis[14] and hypovolemia [15-17] may be central to the pathophysiology.” This statement is correct as written, but reference 14 is nearly 20 years old and so the phrase “more recent” is not really very accurate. You could improve this sentence by referring to the work of cited below which is indeed more recent (2013), which covers far more data than that provided in the cited references, and which supports your finding that respiratory distress is highly correlated with lactic acidosis. Reference is: Cserti-Gazdewich CM, Dhabangi A, Musoke C, et al. Inter-relationships of cardinal features and outcomes of symptomatic pediatric Plasmodium falciparum malaria in 1,933

RESPONSE
We have substituted “more recent” with “subsequent” as we think it is important to cite the 1996 paper by Mike English et al, which was one of the first to challenge the pervasive view that respiratory distress in severe malarial anaemia was due to congestive cardiac failure, highlighting instead the importance of metabolic acidosis. We are also happy to cite the more recent work by your group! Thank you for the suggestion.

8) Discussion, Paragraph #3: With the growing access to point-of-care lactic acid measurements, there is the important question of whether an elevated LA helps to further identify those at high risk of death. If it does, then this would be a good argument to further invest in LA measurement for risk stratification. With this in mind, Readers might be very interested to see:
..Among children who present with an Hb < 5 g/dL and who receive transfusion:
LA < 5 mM LA > 5 mM
Dead a b
Alive c d

On the other hand, rather than doing this univariate chi-square, you might prefer simply to report the odds-ratio of elevated lactate in the logistic regression. See point # 3 above.

RESPONSE
We thank the reviewer for this general point about lactate acidosis and risk of mortality. We agree that this is of interest for both critically ill children in general and those specifically with severe anaemia. Acidosis has already been presented as a subgroup analysis (see the appendix of the NEJM paper), and it can been seen there that mortality is higher in those with acidosis (lactate >5mmol/L). Risk factors for mortality have been analysed in this population, and a paper is undergoing final revisions before submission.

9) Discussion, paragraph 6: “As far as we are aware…”. You may want to adjust the text here if the analysis demonstrates (as I suspect that it will) that re-transfusion is highly associated with the presenting level of Hb.

RESPONSE
We have modified the text in paragraph 6 accordingly.

10) Discussion: “The highest proportion of repeat transfusions occurred in Mulago Hospital...” This paragraph is weak, not fully supported by the data, and I urge you to reconsider the message. You do NOT present data demonstrating superiority of whole blood over packed cells. The suggested logistic regression (see above) could include that variable to demonstrate whether or not there is a statistically meaningful association between survival and whole blood vs packed RBCs...as well as demonstrate the magnitude of the effect. Unless you are armed with such data, I would recommend AGAINST speculation in this section that whole blood brings advantages. In fact, from a strictly transfusion medicine perspective, the opposite can be argued. Consider the following points:
* Making packed cells does NOT add much cost at all. Most regional blood suppliers have a centrifuge and, even without a centrifuge, one can make packed RBCs by simple gravity sedimentation overnight by placing the bags in a vertical posture.
* Your data demonstrates that for ANY level of Hb worthy of transfusion, that the bolus group did less well. Thus excess volume is NOT an advantage to these
children and so it may not be wise to promote whole blood without better data to support it.

* Your data very strongly demonstrates that “time” is of the essence for saving lives among the severely anemic. This is a very strong a powerful data point. Seeing this fact, as a Transfusion Medicine professional, I would want to have Group O Red Cells available at all times in my pediatric urgent care area because the child who arrives at 6 pm may not make it until morning without transfusion. However, whereas group O packed RBCs can really be given to nearly every child without much risk, group O whole blood carries anti-A and anti-B antibodies in the plasma. These antibodies can “add” to the hemolysis if the recipient is group A or group B or group AB. This is especially a greater risk in children (compared with adults) where the relative volume of donor blood is high. Hemolysis contributed to by passive transfer of anti-A and anti-B from the group O whole blood bag is often hard to observe in patients who present with hemolytic conditions (like malaria) and so you could miss it. As a result, in regions where whole blood is used, blood bank professionals prefer to provide “ABO matched whole blood” rather than “emergency group O”. In contrast, when working with packed RBCs, facilities provide “group O packed RBCs for all”. It is, of course, far easier to maintain an “emergency inventory” of just one blood group. Emergency inventories of group O packed RBCs do not require ABO typing the recipient or crossmatching and so delay in therapy “after hours” is less likely to occur. For all these reasons, if I were setting up an “emergency transfusion” scheme in sub-Saharan Africa, it would be far easier to defend the use of “Group O packed RBCs” as the initial management product.

RESPONSE
Thank you for these interesting observations. The analysis we present indicates that more transfusions are given at Mulago - probably since they have a very good supply of blood from the National Transfusion service. To reduce the length of the Discussion section, we have removed the subsequent paragraph that discusses the pros and cons of transfusing with packed red cells.

We note that you advocate use of emergency group O blood. One of the study investigators has enquired with a number of transfusion centres as to whether they would support this policy – and all have stated they would not. They maintain that the rate-limiting step is not cross match (which takes less the 15 minutes), but delayed referral and a lack of triage of those at highest risk of dying.

11) Discussion, end of the paragraph referred to in #10 above: “the paucity of serious adverse events…” I would first check the chi-square analysis referred to above in item # 2.

RESPONSE
Please see our response (above) to # 2.

12) Discussion: “The high proportion of repeat transfusions also…” I think this is a bit self-serving and not fully supported by the data. See discussion above. You can refine this for Readers, I think, by pointing out that re-transfusion is really a topic for those who present with extreme anemia. You might want to be a bit more conservative in your comments here. I do not think that we have good clinical outcomes data on children who present with Hb’s of 1-3 g/dL (really severe anemia). These children, who often have systemic acidosis and thus a cardio-depressant effect of low pH, are fragile recipients. We do not have sufficient clinical research data to know that 30 mL/kg is safe for this sub-set. It may be that they are better treated with repeated lower dose transfusions. If I
were writing this section, I would rephrase this to make the following points:
* Repeat transfusions are more likely in those who present with extreme anemia.
* The ideal volume and rate of red cell replacement for patients with extreme anemia is unknown and deserves further study.

**RESPONSE**

Please see our response in relation to # 4b, namely the high proportion of children in this study that required re-transfusion. We agree with your comments and fully appreciate the need for caution in relation to transfusion of children with “extreme anaemia” (Hb <3g/dl) with 30mls/kg of blood, and have modified the wording of this paragraph accordingly.

Preliminary evidence suggests that transfusion of children with haemoglobin <6g/dl (median Hb 4.2g/dl, IQR 3.1 to 4.9) with 30mls/kg whole blood is safe (see reference 37: Olupot-Olupot et al; BMC Medicine 2014). The safety of this increased transfusion volume is being closely monitored in children with Hb <6g/dl (a proportion of whom will have admission Hb <3g/dl) within the context of a large (n=3954) on-going clinical trial in Africa (TRACT: ISRCTN84086586). TRACT is following UK transfusion adverse event reporting guidelines, which document all cases of pulmonary oedema, transfusion related acute lung injury (TRALI) and transfusion associated cardiac overload (TACO).

**Minor issues not for publication:**

Results: Furosemide is mis-spelled.

**RESPONSE**

Our manuscript has used English spelling (hence frusemide instead of the American furosemide)

**Summary**

Finally, I would like to congratulate the authors of this paper on this fine work. Anemia in children is an extremely important topic in sub-Saharan Africa. This group has distinguished itself as leaders in the effort to do pragmatic clinical research that will benefit millions of children worldwide. I hope that each and every author of this work is proud of this effort and that you know how grateful are Readers for the insight gained from these important results. I would like to also thank the Editors for the privilege of being allowed to review this important manuscript.

**RESPONSE**

Thank you!

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests.
Reviewer’s report
Title: Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness
Version: 1 Date: 23 September 2014

Reviewer: John Myburgh

Reviewer’s report:
This is another high quality analysis from the landmark FEAST trial. This paper follows the previous publication of transfusion volumes in Ugandan children and is a comprehensive and detailed analysis of transfusion practice, thresholds and outcome in patients who were transfused in FEAST. The most important aspect of this trial is an assessment of compliance with WHO transfusion guidelines from a specific geographical (low-income) region that will draw substantial commentary questioning the external validity of the results. The hypothesis and objectives are clear and explicit. It is not stated whether this post hoc analysis was pre-specified before or during FEAST. Overall, the methods are sound, well described and accurately presented, although there is extensive space and words given to describe the methods used in FEAST. As an understanding of FEAST is essential in interpreting this post hoc study, this section should be substantially shortened with a reference to the New England Journal of Medicine publication.

RESPONSE
We have been advised by BMC Medicine to retain the methodological details of the FEAST trial in this paper, since their preference is that this could be read without the need to cross reference NEJM paper.

The methods used to define and analyse variables defined in this paper should only be presented in this paper. Specifically, a number of methods or definitions are presented in the results section, eg nutritional status and quantification of parasitaemia. These should be clearly defined in the methods section (that can be substantially shortened) and this will make the results section easier to read.

RESPONSE
We have now minimised any repetition of definitions.

A key objective of this analysis is to determine compliance with WHO guidelines – while these and other jurisdictional guidelines are summarised in Table 1, an assessment of compliance with these should be presented in the methods section and included in the results.

RESPONSE
We have examined adherence to WHO guidelines by means of our analysis of clinical predictors of transfusion and re-transfusion.

The Forest plot definitions outlined in the methods are not the same as presented in the results – these need to be consistent – either define these according to haemoglobin cut off level (as presented) or by severity of anaemia (as is
presented throughout the paper). My recommendation is the latter.

**RESPONSE**

We feel that it is important to present the impact of the fluid boluses at all levels of haemoglobin as this is something that is frequently asked to the study group. We have also created a Forrest plot of the same outcome using the four anaemia categories.

The results are very long and there is an extraordinary large amount of data presented. As indicated above, this section can be substantially shortened by removing methodological definitions and details description of data that are clearly presented in the tables, particularly clinical characteristics (table 2) and site data (table 3). Similarly, the data presented in table 4 is clear and the information presented in the results section can be substantially shortened to focus on the clear positives and negatives.

**RESPONSE**

We feel that a written description (in addition to the Tables) is easier for the reader to follow, although we have now minimised redundant text and unnecessary repetition of definitions.

The KM graphs should be redone and simplified to show the probability of starting a transfusion for the 3 groups of patients according to Hb - this is a key outcome of this analysis. The site data for each group can be presented in tabular form or as supplemental material. It is not clear why only two groups are presented in the KM graphs.

**RESPONSE**

We had initially presented only KM graphs for the two groups with haemoglobin <10 as these are the groups that have the majority of the transfusions. We have now edited the figure so all four groups are represented.

Similarly, the discussion needs to be extensively revised and substantially shortened to focus on the objective and aim of this important analysis. There is substantive repetition of the results and the inclusion of new results within the discussion section. This section needs to solely focus on a statement of principal findings written factually without editorial commentary, a summary of these findings to high-quality published literature, a summary of weaknesses and strengths, that should include a statement about generalisability and applicability of these results, implications for clinicians and policy makers, specifically a comment about the lack of compliance to WHO guidelines and potentials for this and a stronger statement about potential future research that includes the investigators phase III trial.

**RESPONSE**

We have shortened and revised the discussion.
Major compulsory revisions:
1. Substantially shorten the description of the FEAST methods and specifically define methods applicable to this analysis in the methods section.
2. Include an analysis of determination of compliance to the WHO Guidelines
3. Revise the KM graphs to present only the groups per Hb level
4. Standardise the Forest plot to the same as the FP data
5. Substantially shorten and revise the discussion and outlined and remove redundant and editorial commentary.

Minor essential revisions:
State whether this analysis was pre-specified before or during FEAST

RESPONSE
We have now included this in the statistical section of the Methods

Discretionary revisions:
1. Nil