Author’s response to reviews

Title: Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial

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Version: 3
Date: 24 February 2015

Author’s response to reviews: see over
24th February 2015

Dear Sir/Madam

Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial

Please find attached the above revised protocol paper following the reviewers comments received on the 7th January 2015.

We would like to thank the reviewers for their time and valuable comments. We have responded to all the comments (please see below) however, we did not add all the information to the paper since we believe it will be more relevant to the result paper that we plan on publishing when the trial has finished recruiting and the data is analysed. As you are aware the protocol paper addresses how the trial is conducted while the full paper will discuss the results and address the comments below.

Yours faithfully
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Reviewer's report

Title: Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial

Version: 2 Date: 23 December 2014

Reviewer: Simon Stanworth

Reviewer's report:
This is a well written paper describing the rationale and detail for a randomized trial of targeted concentrated fibrinogen infusion, using concentrate. Could the background be shortened and focussed on the condition (PPH), the intervention, and the need for research. It is important to cross-reference to any relevant systematic reviews of the intervention.

There are no systematic reviews of the use of fibrinogen concentrate in PPH and we now stated this in the introduction.

Are any other trials of fibrinogen in PPH completed and any differences in design?
One study has been completed but the results have not been published at the time of writing (NCT01359878).

The authors indicate delays e.g. turnaround times for testing and blood components, but other groups have published on alternative strategies to minimise eg to reduce laboratory times for testing, or pre-thawed plasma.
The turnaround times quoted were from an internal audit and indicated the time from the blood test to when the result reached the clinician. Although some specialised groups have reported improvements in turn round time, as stated by the reviewer, in the real world we think these times are a fair reflection. Irrespective of the actual times no laboratory based test would come close to the 10 minutes seen with Fibtem A5.

Compared to other data, the reported confidence intervals for many of the results presented in the background actually seem quite narrow eg measures of bleeding, transfusion, testing.
The confidence intervals come from 12 months prospectively collected data from one institution. We accept that they may be larger if multicentre data were used.

The main trial objective is well described. Could the authors provide justification for use of blood products as main outcome – data from cardiac surgery and trauma suggest general limitations to the use of reduction in transfusion needs as main endpoints.
Blood products use can be definitively measured in contrast to bleed volume which is very difficult to measure in a standardised way. If hysterectomy or mortality was used then a very much large sample size would have been needed because this event is so rare (see response to reviewer 2).
This study is looking for an efficacy signal and if successful a much large study investigating more clinically relevant endpoints can be designed.

The sample size calculation is not easy to follow, but reflects the issues of means and different scales.
I would be happy to simplify the sample size if helpful.

Should the primary outcome just look at red cell requirements (see next point)?
The use of RBC requirement alone has the drawback that the starting Hb heavily influences this i.e. the lower the antenatal Hb the more likely a woman is to be transfused red cells. Also Hb does not reflect any treatment of coagulopathy (ie FFP and cryo) and so we prefer to use total allogeneics as the primary outcome and report other outcomes as secondary.

Please add some justification for the clinical meaningfulness for the expected differences in use of blood.
The study is looking for an efficacy signal and if successful a study powered to investigate other outcomes can be devised. It would not have been feasible to performed a study power eg on hysterectomy because the sample size would have been unfeasibly large and no funder would have supported it without prior evidence of potential efficacy. This study is part of a stepwise research programme.

How will the authors deal with protocol violations/deviations?
All important protocol deviations or violations will be described in full (e.g. ineligible participants included in the trial, non-compliance, withdrawals, loss to follow up). Ineligible patients recruited into the trial will be excluded. All analyses will be based on the intention to treat principle. Any protocol deviations that result in missing data (such as loss to follow-up) will be analysed as such with a sensitivity analysis imputing for missing values. Deviations concerning treatment compliance will be addressed using Complier-average causal effect (CACE) analysis. This will be detailed in the statistical analysis plan.

Crucial to interpretation of blood use will be operational aspects and blinding.
What resources are required to deliver on this trial – and how does this operate out of routine hours? How much will this affect ‘routine’ practice and standard procedures, and crucially the decision to give FFP?
The reviewer correctly implies that this is a highly complex clinical situation and running a blinded CTIMP enrolling acute sick subjects whilst ensuring safe management is challenging. The safety of patients is of course paramount and clinicians on the ground must decide whether it is safe to enrol subjects.

Randomisation requires two clinicians to be available, one to manage the patient and one to perform the randomisation. Out of hours randomisations are occurring within the study and a screen log is submitted weekly by each
centre so that it is known whether eligible subjects have been missed and the reasons for not recruiting, that information will be included in the study report.

Units follow the same standard massive obstetric haemorrhage protocols within and outside working hours. The decision to give FFP is at the discretion of the treating consultant and unlikely to be affected by working hours. The decision is made at consultant level to reduce the variability of decision making of more junior clinicians. Despite this, variability of practice across centres and between clinicians is to be expected and is an important aspect of a multicentre study if the study results are to be generalizable.

Has any consideration been given to testing the success of blinding? The success of the mechanism for blinding was assessed by St Mary’s Pharmaceutical Unit before the study started and found to be suitable. We added this information to the paper.

The discussion should also mention perceived limitations of the study. Have any (or no) subgroup analyses been pre-specified? There will be one subgroup analysis to look at women randomised with a Fibtem A5 <10mm.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests: I have no competing interests

Reviewer’s report
Title: Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial
Version: 2Date:6 January 2015
Reviewer: Johanna van der Bom

Reviewer’s report: Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial by Aawar et al. The manuscript describes the protocol for a randomised controlled trial comparing the effect of fibrinogen concentrate versus placebo on number of allogenic blood products transfused after the study medication among women with low fibrinogen levels – assessed by Fibtem A5 < 16 mm which is about 3 g/l.

1. Will the study design adequately test the hypothesis? The authors formulate the aim “The aim of the study is to investigate whether
infusion of fibrinogen concentrate, based on the Fibtem A5 test, during a moderately severe PPH reduces the total number of allogenic blood products transfused after study medication until discharge compared to placebo”.
I could not find a clear hypothesis. From the text I deduced that the study will test the following hypothesis “the infusion of fibrinogen concentrate with a target Fibtem A5 level of at least 23 mm among women suffering ongoing PPH and a Fibtem A5 below 16 mm reduces the total number of allogenic blood products transfused after study medication until discharge compared to placebo.”

The assumed hypothesis is correct.

There are some limitations of the current design that will affect the findings and inferences. Most of these limitations are also recognised and discussed by the authors.

a) Blinding is only achieved until after the decision to give the first 4 units of FFP.
The actual outcome will occur after this moment and this unblinding can/will lead to a different transfusion strategy for the two intervention arms. It is therefore no longer possible to infer that a possible observed difference between the intervention arms is purely the result of the intervention; it may also be the result of the clinician’s believe in an effect of the intervention. This may lead both to an over- and underestimation of the obtained estimate of effect.
Any study needs to put the safety of subjects above all other considerations. If clinicians were not able to know the actual fibrinogen levels after the first FFP had been infused then there is no doubt that women would be put at increased risk.

The knowledge of the post FFP fibrinogen level does not necessarily unblind the study. Because of ongoing consumption and dilution and the effect of FFP replacement it may not be obvious whether placebo or fibrinogen has been given. The knowledge of the actual fibrinogen is however critical to patient safety.

We are convinced that we have made an appropriate decision on this issue based on patient safety considerations.

b) A clinician can decide to access the results of the Fibtem and coagulation screen that is measured 15 min after randomisation even before the decision to give the first 4 FFP units. If this happens the investigators plan to exclude this woman from the primary efficacy analysis. This hampers exchangeability between intervention arms and interferes with the planned intention-to-treat analysis.

As above subject safety is paramount. The study randomises women experiencing potential life threaten bleeding. The protocol allows the clinician on the ground to see the 15 min Fibtem A5 and act on it if, in their opinion, not to do so puts the woman at risk. In our view this is an important safety aspect.
of the protocol. So far 40 women have been randomised and in no case has the 15 minute Fibtem been viewed before the FFP decision point.

As with (a), we acknowledge the reviewer’s point with regards to purity of trial design but subject safety must take precedence.

c) What do the investigators do to prevent allocation concealment? At the time of randomisation the next consecutive study pack will be opened. Given the block size, is it possible to predict the next intervention?
Two blocks sizes were used to minimise the risk of subversion and the potential for imbalance. Within a site, a particular block size was chosen at random and another used to randomly select a particular block arrangement, which set the allocation order. To further minimise risk of concealment, the detail of the blocks sizes are not known to any of the investigational team and are only detailed in the randomisation protocol.

d) Even if the hypothesis is adequately tested it is important to consider the following limitation of the current design. The ultimate aim of infusion of fibrinogen concentrate is of course the prevention of PPH related morbidity, such as mortality and hysterectomy. Yet, the endpoint of the study is total number of allogenic blood products. The assumption is that more allogenic blood products is related to higher morbidity. This assumption may not be met in the case of mortality or in the case of earlier hysterectomy. Thus, fewer allogenic blood products could be more severe than more allogenic blood product. Given the secondary endpoints the investigators will be able to examine the presence and eventual consequences of such survival bias.

It is not feasible to power this study based on mortality or hysterectomy. The mortality from PPH in the UK is 0.49/100 000 maternities. Therefore based on national data we would expect to see 1 death every 8 years in the 4 participating centres combined. In the study so far there have been 40 randomisations and no hysterectomies and no deaths. Hysterectomy is a late intervention for PPH and so it is unlikely to be associated with reduced transfusion requirement. We do not think, therefore, that early hysterectomy or early death will be a significant issue that will affect the analysis due to survivor bias, in contrast to the situation for massive or military trauma where death is common. We will use the secondary outcomes to check for this in the analysis as suggested by the reviewer.

The trial is looking for an efficacy signal and if successful a much larger study based on the clinically important outcomes suggested by the reviewer will be designed.

e) With total number of allogenic blood products as primary endpoint, it is important to standardize the strategies to transfuse all allogenic blood products.

In the manuscript I missed a standardized protocol for transfusion of allogenic
blood products. Only in the discussion the investigators mention “the first 4 FFP units”. What are the triggers and prescribed doses of red blood cells, FFP, cryo and platelets? Are they similar in the participating clinics?

The protocol for transfusion of blood products is include in the protocol in section 10.5.3 and clarified this in the paper.

f) Is it true that according to the study protocol infusion of FFP will be postponed until after observing a Fibtem A5 under 16 mm? Does this mean that the investigators plan not to prevent, but instead to await coagulopathy.

Given their experience I am convinced that they find Fibtem A5 an acceptable value for women with PPH. It would be worthwhile to discuss this in the discussion section.

This is a study looking at early intervention and the randomisation point is before a coagulopathy has developed. In 356 prospectively collected cases (Collins et al Blood 124:1727-36, 2014) all women with Fibtem A5 >15 mm had normal PT and aPTT. Therefore there is no evidence of coagulopathy in women with Fibtem A5 >15 mm.

2. Is the planned statistical analysis appropriate?
Yes, the planned statistical analysis is appropriate.
It would be interesting to find a list (and predefined categories) of baseline variables that are considered to be included in the model that adjusts for baseline imbalances.

Baseline variables that will be summarised and examined for imbalance between arms will include: Age at recruitment, ethnicity, weight/height (BMI), gestation at birth, gravida, parity, previous C-sections, history of PPH, pregnancy related complications, anticoagulation medicine (aspirin and LMWH) given before birth, labour (induced or spontaneous), use of syntocinon, single or multiple birth, trauma, anaesthetic procedures.

Are there any subgroup analyses planned?
Yes, the subgroup with a Fibtem A5 <10 mm will be analysed.

3. Are sufficient details provided to allow replication of the work or comparison with related analyses; if not, what is missing?

a) Standardisation of the triggers for RBC, FFP, cryo and platelet transfusion is missing.

We added this information to the paper.

b) What is the definition of secondary postpartum haemorrhage?
Secondary PPH is defined as abnormal bleeding starting between 24 hours and 6 weeks after delivery.

4. Is the writing acceptable?
Yes.