PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a phase 3, non-inferiority, randomized comparison of a new fibrinogen concentrate vs. cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients: the FIBRES trial
AUTHORS	Karkouti, K; Callum, Jeannie; Rao, Vivek; heddle, nancy; Farkouh, Michael; Crowther, Mark; Scales, Damon

VERSION 1 – REVIEW

REVIEWER	Lucy Yang University College London Hospitals Intensive Care Unit United Kingdom
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	Very good study in general, and extremely relevant. My main concern is that consenting patients post op whilst they may be recovering from anaesthesia / bleeding significantly, they may not be at maximum capacity for making a decision to enter a research trial. It may be helpful to pre-emptly consent patients, but only include those who were randomised in the analysis. The other issues are that the inclusion criteria does not seem detailed enough to define 'significant bleeding' and hypofibrinogenaemia. Please address these. Please also give slightly more detailed comparison on statistics, and clarify whether this has been reviewed by an independent statistician. Detailed comments in PDF. - The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Christian Fenger-Eriksen Department of Anaesthesiology Aarhus Universityhospital Nørrebrogade, DK-8000 Aarhuc C Mobil + 45 2636 2416 25-Jan-2018
REVIEW RETURNED	Review: BMJ open-2017-020741, entitled "Protocol for a phase 3, non-inferiority, randomized comparison of a new fibrinogen concentrate vs. cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients: the FIBRES trial." The present manuscript by Karkouti and colleagues constitutes a protocol for a randomized controlled trial comparing a new fibrinogen concentrate vs. cryoprecipitate for treating acquired

	hypofibrinogenemia in bleeding cardiac surgical patients. Although company financed the scope of the study and the randomized, controlled study design is based on an excellent clinical idea, as high quality studies in this area is highly requested. From a European perspective however the choice to include cryoprecipitate as a comparator may be questionable as this product is more or less obsolete. Fibrinogen concentrate 4 g is compared to cryoprecipitate 10 units (300 – 400 ml). The authors present no data to support that these doses are comparable. It seems that amount of fibrinogen infused in the cryo group may be higher. Are no direct evaluation of treatment included as secondary endpoint ie fibrinogen level ? Inclusion criteria is accepted clinical guideline-driven standards (significant hemorrhage and known or presumed acquired hypofibrinogenemia. This approach seems very pragmatic and may cause difficulties during the analysis phase of their results. Suggest to specify which guidelines are adhered to – and to further define level of hypofibrinogenaemia as many guidelines differ in that question. Further what is meant by “presumed hypofibrinogenaemia” “Efficacy and safety will be evaluated” – please specify which parameters of safety is evaluated. Sample size calculation is based on previous data from the authors with a mean administration of 16 units (SD 14). This seems as a high transfusion rate, taken the study period into account. No definition of treatment / transfusion regimen in the prestudy period (until termination of CPB) has been described in the protocol. Are transfusion algorithms comparable throughout the 12 study centers, please add

VERSION 1 – AUTHOR RESPONSE

Re: Manuscript submission BMJ Open-2017-020741:

“Protocol for a phase 3, non-inferiority, randomized comparison of a new fibrinogen concentrate vs. cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients: the FIBRES trial”
Keyvan Karkouti, Jeannie Callum, Vivek Rao, Nancy Heddle, Michael E Farkouh, Mark Crowther, Damon C Scales

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19-Feb-2018

REVIEWER 1
Dr. Lucy Yang

Very good study in general, and extremely relevant. My main concern is that consenting patients post op whilst they may be recovering from anaesthesia / bleeding significantly, they may not be at maximum capacity for making a decision to enter a research trial. It may be helpful to pre-emptly consent patients, but only include those who were randomised in the analysis.

Response:
We thank Dr. Yang for her positive comments and constructive review of the manuscript. As Dr. Yang notes, many patients who end up receiving cryoprecipitate or fibrinogen concentrate have generally undergone complex surgeries associated with major blood loss and often are not able to provide informed consent until 2–3 days after surgery. Consequently, we have put in place specific procedures in the protocol to ensure informed consent is obtained as soon as possible after surgery.

On page 14, we now specify: *"...written informed consent for follow-up and use of the patients' data will be obtained within 24–48 hours after randomization. If the patient is not capable of providing informed consent, consent will be sought from the surrogate decision maker. Patients will then be re-visited every few days up to postoperative day 28 to obtain their direct consent where possible."*

As we have discussed in the protocol, obtaining consent from patients before surgery is possible but impracticable (page 14), which led to our decision to seek waiver of consent prior to randomization.

The other issues are that the inclusion criteria does not seem detailed enough to define 'significant bleeding' and hypofibrinogenaemia. Please address these.

Response: Our goal was to conduct a very pragmatic trial in order to compare the two products in as close to the real world setting as possible. Hence, we did not attempt to define significant bleeding. For clarity, we have re-worded the eligibility criteria as (page 6): *"The study will enroll all adult patients undergoing cardiac surgery with CPB for whom fibrinogen supplementation is ordered by the clinicians in response to post-CPB hemorrhage in the presence of confirmed or suspected acquired hypofibrinogenemia (fibrinogen level <1.5–2.0 g/L)."*

Please also give slightly more detailed comparison on statistics, and clarify whether this has been reviewed by an independent statistician. Detailed comments in PDF.

Response: The analysis plan has been developed by an independent statistician. More detail has been added (pages 12 and 13).

Dr. Yang's questions marked on the manuscript:

Page 4 Introduction: Referring to fibrinogen levels: Is this below 1.5 or below 2.0? British Haematological society suggest 1.5, but fg likely affects bleeding as a continuum, not as a blanket level... http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2141.2003.04256.x/full

Response: We agree that the issue is one of continuum rather than a strict threshold. We have not included that specific article because it does not address surgery. Recent European guidelines for management of bleeding suggest a trigger of <1.5–2.0 g/L (Rossaint et al. Critical Care 2016;20:100). Similarly, the European Society of Anaesthesiology guidelines for management of severe bleeding recommend treatment at a fibrinogen level of <1.5–2.0 g/L (Kozek-Langenecker et al. Eur J Anaesthesiol 2017;34:3320395).

Page 4: Suggested to add the following reference: Yang L, Vuylsteke A, Gerrard C, Besser M, Baglin T. Post-operative fibrinogen level is associated with post-operative bleeding following cardiothoracic surgery and the effect of fibrinogen replacement therapy remains uncertain. J Thromb Haemost 2013 Aug; 11(8): 1519-26

Response: We have added the reference (page 4). Thank you.

Page 7: Referring to the primary outcome: Please define transfusion to what target, e.g. whether this is haemodynamic stability? Hb between 7g/dL and 9g/dL?? and what platelet level,

Response: Being a pragmatic study, there is no enforcement of transfusion targets. We are, however, capturing detailed laboratory data and will therefore be able to determine if transfusion targets were similar between the two groups.

Is there a research ethics board number? And is this registered on clinicaltrials.gov? If so, include the reference.

Response: The REB and registration information have been added (page 14).

REVIEWER 2
Dr. Christian Fenger-Eriksen

The present manuscript by Karkouti and colleagues constitutes a protocol for a randomized controlled trial comparing a new fibrinogen concentrate vs. cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients.
Although company financed the scope of the study and the randomized, controlled study design is based on an excellent clinical idea, as high quality studies in this area is highly requested.

From a European perspective however the choice to include cryoprecipitate as a comparator may be questionable as this product is more or less obsolete.

Response: We thank Dr. Fenger-Eriksen for his very positive comments regarding the design and clinical importance of our study. Although much of Europe has switched from cryoprecipitate to fibrinogen concentrate, cryoprecipitate remains the standard source of fibrinogen in the UK, Australia, and North America. It is also important to note that Europe switched to fibrinogen concentrate without supporting evidence from high-level clinical trials. Thus, the findings of this trial should also be relevant to European countries.

Fibrinogen concentrate 4 g is compared to cryoprecipitate 10 units (300 – 400 ml). The authors present no data to support that these doses are comparable. It seems that amount of fibrinogen infused in the cryo group may be higher.

Response: The dosing information comes from the Canadian Blood Services internal quality control data. Values and a reference has been added (page 6)

Are no direct evaluation of treatment included as secondary endpoint ie fibrinogen level ?

Response: A secondary efficacy outcome is change in fibrinogen concentration, measured within 75 minutes before and after completion of the first dose of fibrinogen concentrate or cryoprecipitate (page 7).

Inclusion criteria is accepted clinical guideline-driven standards (significant hemorrhage and known or presumed acquired hypofibrinogenemia. This approach seems very pragmatic and may cause difficulties during the analysis phase of their results. Suggest to specify which guidelines are adhered to – and to further define level of hypofibrinogenaemia as many guidelines differ in that question. Further what is meant by “presumed hypofibrinogenaemia”

Response: As we have noted above, our goal was to conduct a very pragmatic trial in order to compare the two products in as close to the real world setting as possible. Hence, we did not attempt to define significant bleeding and will include any patient as long as they are bleeding and their clinicians suspect that acquired hypofibrinogenemia is a contributor to bleeding. For clarity, we have re-worded the eligibility criteria as (page 6): *“The study will enroll all adult patients undergoing cardiac surgery with CPB for whom fibrinogen supplementation is ordered by the clinicians in response to post-CPB hemorrhage in the presence of confirmed or suspected acquired hypofibrinogenemia (fibrinogen level <1.5–2.0 g/L).”*

Regarding fibrinogen level treatment levels, please see our response to Reviewer 1 above.

“Efficacy and safety will be evaluated” – please specify which parameters of safety is evaluated.

Response: We refer the reviewer to the ‘Outcomes and study duration’ (page 7) and ‘Data analysis plan’ (pages 12 and 13) sections, where more detail is provided.

Sample size calculation is based on previous data from the authors with a mean administration of 16 units (SD 14). This seems as a high transfusion rate, taken the study period into account.

Response: The data is obtained from the TACS trial (Karkouti et al. Circulation 2016;134:1152-1162), which was a large multicenter trial that included many of the sites that are participating in this trial. The study was conducted recently, including patients undergoing cardiac surgery during 2014 and 2015. While the amount of transfusions is large, it is important to note that these are patients who received cryoprecipitate, which is generally not used until after substantial blood loss. We have added further details regarding the use of this data in the sample size calculation (page 7).

No definition of treatment / transfusion regimen in the prestudy period (until termination of CPB) has been described in the protocol.

Response: CPB conduct will be according to institutional standards. Importantly, standard CPB practice is highly regimented within sites and to a large extent across sites. The primary outcome of the study is post-CPB transfusion, so across site variability should have little impact. Nevertheless, stratified randomization by site (page 8) should further minimize the impact of site on outcomes.

Are transfusion algorithms comparable throughout the 12 study centers, please add

Response: The principles of bleeding management in cardiac surgery are relatively consistent across sites, but we do know that there is variability in practice and transfusion rates across sites (as was shown in the TACS and other trials). We also know that trying to standardize clinical practice is fraught with problems and leads to unacceptably high protocol violations. Hence, we chose to maintain the pragmatic approach and allowed each site to maintain their standard of care. In anticipation of this variability, we now state (page 8): *"As transfusion practice is not standardized, randomization will be stratified by study site."*

VERSION 2 – REVIEW

REVIEWER	Christian Fenger-Eriksen Department of Anaesthesiology Aarhus Universityhospital Nørrebrogade, DK-8000 Aarhuc C Denmark
REVIEW RETURNED	13-Mar-2018

GENERAL COMMENTS	Dear Dr. Keyvan Karkouti All my concerns have been properly adressed by the authors. I have no more comments and will be looking forward to result of this interesting study.