BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020741
Article Type:	Protocol
Date Submitted by the Author:	21-Nov-2017
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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Cardiac surgery < SURGERY, Clinical trials < THERAPEUTICS, Blood bank & transfusion medicine < HAEMATOLOGY, HAEMATOLOGY

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

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Word count: 3,410

Keywords: Bleeding disorders and coagulopathies; Cardiac surgery; Clinical trials; Adult surgery; Blood bank & transfusion medicine; Haematology

ABSTRACT

Introduction: Coagulopathic bleeding is a serious complication of cardiac surgery to which an important contributor is acquired hypofibrinogenemia (plasma fibrinogen <1.5–2.0 g/L). The standard intervention for acquired hypofibrinogenemia is cryoprecipitate, but purified fibrinogen concentrates are also available. There is little comparative data between the two therapies and randomized trials are needed.

Methods and analysis: FIBrinogen REplenishment in Surgery (FIBRES) is a multi-centre, randomized (1:1), active-control, single-blinded, phase 3 trial in adult cardiac surgical patients experiencing clinically significant bleeding related to acquired hypofibrinogenemia. The primary objective is to demonstrate that fibrinogen concentrate (Octafibrin/Fibryga, Octapharma) is non-inferior to cryoprecipitate. All patients for whom fibrinogen supplementation is ordered by the clinical team within 24 hours of cardiopulmonary bypass will receive 4 g fibrinogen concentrate or 10 units of cryoprecipitate (dose-equivalent to 4 g), based on random allocation and deferred consent. The primary outcome is total red cell, platelet, and plasma transfusions administered within 24 hours of bypass. Secondary outcomes include major bleeding, fibrinogen levels, and adverse events within 28 days. Enrollment of 1,200 patients will provide >90% power to demonstrate non-inferiority. A pre-planned interim analysis will include 600 patients. The pragmatic design and treatment algorithm align with standard practice, aiding adherence and generalizability.

Ethics and dissemination: The study is approved by the local research ethics board and will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and regulatory requirements. Patient consent prior to treatment is waived, as per criteria in the Tri-Council Policy Statement. Results will be published in the scientific/medical literature, and at international congresses. Non-inferiority of purified fibrinogen concentrate would support its use in acquired hypofibrinogenemia. The results are likely to improve care for cardiac surgical patients experiencing significant bleeding, an under-studied yet high-risk population.

Trial registration: NCT03037424 (ClinicalTrials.gov).

Word count: 294 (max. 300 words)

STRENGTHS AND LIMITATIONS OF THIS STUDY

[Up to 5 bullets, no longer than one sentence each, each relating to the methods]

- This is the largest randomized comparison of fibrinogen concentrate versus cryoprecipitate in adult patients with acquired hypofibrinogenemia due to cardiac surgery involving cardiopulmonary bypass.
- Simple, pragmatic study design and use of a treatment algorithm that aligns with standard clinical practice will enhance adherence and ensure clinical relevance and generalizability.
- Use of an active control, cryoprecipitate, as the comparator guarantees that all patients in the study will receive fibrinogen supplementation as clinically indicated.
- The large sample size of approximately 1,200 patients in this high-risk population will provide >90% power to detect non-inferiority of fibrinogen concentrate to cryoprecipitate.
- It will not be possible to fully blind clinicians to treatment allocation, so all outcome assessors will be blinded to minimize the risk of bias.

INTRODUCTION

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in approximately 10% or more of cases, it often requires massive blood transfusion with allogeneic blood products (ABPs), and is associated with an increased risk of serious postoperative adverse outcomes, including sepsis, renal failure, and death.[1-4] While the causes of coagulopathy in this setting are likely to be multifactorial, acquired hypofibrinogenemia, considered as a deficiency in plasma fibrinogen levels below 1.5–2.0 g/L,[5] is believed to be one of the primary factors.[6]

Fibrinogen is the most abundant clotting factor in the human circulation and plays a pivotal role in hemostasis and the coagulation cascade by promoting clot formation and platelet aggregation.[7] Physiological levels of fibrinogen are typically in the range of 1.5–4.5 g/L,[8] with a half-life following synthesis of approximately four days.[9] A number of factors may contribute to the development of acquired hypofibrinogenemia in cardiac surgery. Fibrinogen loss may result from acute bleeding, dilution of the circulatory volume due to administration of fluids and priming of the CPB circuit, and consumption due to activation of the coagulation cascade during CPB.[10] Since fibrinogen has only a limited reserve in the body, a modest decrease in levels to <1.5–2.0 g/L impairs coagulation and increases the likelihood of bleeding complications.[10-14] Fibrinogen levels have been shown to fall 40–50% during cardiac surgery,[10] with a critical drop observed in approximately 5% of patients.[15] In these patients, fibrinogen supplementation is believed to be essential and is the current standard of care in most jurisdictions.[6,16]

While supplementation of fibrinogen has historically included the use of fresh frozen plasma, the two principal options currently recommended for supplementation in acquired hypofibrinogenemia are cryoprecipitate and purified fibrinogen concentrate.[5] Cryoprecipitate is currently used in North America and is an ABP prepared from fresh frozen plasma through a process of thawing and centrifugation. The clotting factor-enriched precipitate is resuspended in a small volume of plasma and refrozen. Typical fibrinogen content is around 15 g/L,[17] although this may vary considerably (3–30 g/L) due to inter-donor variability.[18] Cryoprecipitate has largely been withdrawn from most European countries due to safety concerns because it does not undergo pathogen reduction,[19] where treatment with purified human fibrinogen concentrate is the preferred therapeutic choice for hypofibrinogenemia. Fibrinogen concentrate has a number of important advantages over cryoprecipitate, including: significantly higher purity; standardized fibrinogen content, enabling more accurate dosing; faster preparation and administration time; no requirement for blood type matching; and improved safety, particularly through pathogen reduction technology.[6,19-21] Cryoprecipitate remains the most common fibrinogen replacement product in North America and may be a more effective hemostatic agent because it also contains hemostatic factors VIII and XIII, von Willebrand factor, and platelet microparticles.

There is scant data comparing cryoprecipitate and fibrinogen concentrate for the treatment of acquired hypofibrinogenemia; thus, we do not know which of these is the most appropriate therapy in bleeding cardiac surgical patients. Moreover, mounting evidence indicates that hemostatic management of patients with coagulopathic bleeding is evolving from the conventional use of non-purified ABPs to targeted therapeutic algorithms using purified coagulation factor concentrates such as fibrinogen concentrate.[22] There is therefore a need for prospective, randomized clinical trials designed to specifically evaluate cryoprecipitate and fibrinogen concentrate in parallel as part of hemostatic treatment algorithms in bleeding cardiac surgical patients.

Our study design addresses these issues by assessing non-inferiority of a purified fibrinogen concentrate against cryoprecipitate for the treatment of acquired hypofibrinogenemia in cardiac surgery. Given the theoretical and logistical advantages of fibrinogen concentrate relative to cryoprecipitate outlined above, illustrating that fibrinogen concentrate is non-inferior to cryoprecipitate would support the use of this purified fibrinogen concentrate for hemostatic management in this high-risk, clinically important setting. Importantly, the conduct of randomized trials in bleeding surgical patients poses specific challenges, and this trial incorporates several design features to address these challenges.

METHODS AND ANALYSIS

Objective

The primary objective of this study is to demonstrate that the administration of the fibrinogen concentrate Octafibrin/Fibryga (Octapharma AG, Lachen, Switzerland; currently approved in Canada for the treatment of congenital afibrinogenemia and hypofibrinogenemia) is non-inferior to cryoprecipitate for treating bleeding in cardiac surgical patients in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards.

Study design and setting

The FIBrinogen REplenishment in Surgery (FIBRES) trial is a pragmatic, multi-centre, randomized, active-control, non-inferiority phase 3 trial in adult cardiac surgical patients experiencing clinically significant bleeding in whom fibrinogen supplementation is deemed to be necessary. A pragmatic study design was chosen because it allows participating sites and surgical teams to maintain standard clinical practice when treating patients, making the study clinically relevant and generalizable to the large population of patients undergoing cardiac surgery, and increases the likelihood of protocol adherence and successful study completion. Approximately 1,200 patients will be recruited from up to 12 Canadian hospitals. Patients will be randomized when fibrinogen supplementation is ordered to either of two treatment groups: fibrinogen concentrate 4 g (intervention) or cryoprecipitate 10 units (active control). No placebo arm has been included in the trial because withholding effective treatment is neither

consistent with standard practice nor acceptable on ethical grounds. Treatment arm allocation will be maintained for up to 24 hours after completion of CPB surgery; only the randomly-allocated fibrinogen replacement product can be provided during this time. No other aspects of care will be modified. Informed consent will be obtained as soon as possible after surgery. Efficacy and safety will be evaluated. An overview of the study design is presented in ***Figure 1***. The study commenced in February 2017 and is expected to complete in late 2018, with results available in early 2019.

Eligibility criteria

The study will enroll all adult patients undergoing cardiac surgery with CPB for whom fibrinogen supplementation is ordered in accordance with accepted clinical guideline-driven standards (significant hemorrhage and known or presumed acquired hypofibrinogenemia). The exclusion criteria are: receipt of either fibrinogen concentrate or cryoprecipitate within 24 hours before surgery; a history of severe allergic reaction to fibrinogen concentrate or cryoprecipitate; known refusal of either study treatment (*i.e.*, for religious reasons); a known fibrinogen level >3.0 g/L within 30 minutes of the order for treatment (to eliminate the risk of raising a patient's fibrinogen level above the upper limit of the normal range [4.0 g/L]); and known pregnancy.

Interventions

Intervention

Patients randomized to the intervention group will receive fibrinogen concentrate administered by slow (over 10 minutes) intravenous injection immediately after reconstitution with 50 mL of sterile water for injection, as per the manufacturer's instructions. Patients randomized to this group will receive 4 g of fibrinogen concentrate each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB surgery.

Active control

Those patients randomized to the active control group will each receive cryoprecipitate, given as 10 units (dose-equivalent to 4 g, as per internal Canadian Blood Services quality control data; personal communication, Canadian Blood Services) each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB. Cryoprecipitate will be prepared according to current Health Canada standards and administered by intravenous infusion following hospital transfusion policies at each of the participating study sites.

In both study arms, study treatment (fibrinogen concentrate or cryoprecipitate) may be administered prior to the determination of fibrinogen levels in a patient that is bleeding if deemed appropriate as per current clinical standards (*i.e.*, rapid bleeding precluding waiting for laboratory results). If fibrinogen supplementation is needed after the 24-hour study period

is over, patients will receive cryoprecipitate, which is the current standard-of-care in most of Canada. Concomitant medications to treat bleeding that are part of standard patient care will be permitted throughout the study, but must be recorded in the case report form (CRF).

Outcomes and study duration

The primary outcome of the study is one of efficacy; specifically, comparison between study groups of the total number of red cells, platelets, and plasma administered during the first 24 hours after termination of CPB surgery.

Secondary outcomes of the study will include both efficacy and safety outcomes. For the former, the secondary outcomes are: 1) comparison of the total number of ABPs (not including cryoprecipitate) administered from the start of surgery up to seven days after surgery (or discharge if earlier); 2) comparison of major bleeding (using the modified universal definition of perioperative bleeding [UDPB] in cardiac surgery)[23] during the first 24 hours after termination of CPB; and 3) comparison of the effect of treatment on plasma fibrinogen levels, determined by the change from within one hour before to one hour after the first dose of fibrinogen supplementation. The secondary safety outcomes are: 1) adverse events (AEs) and serious AEs (SAEs) up to 28 days postoperatively; 2) a composite AE grouping (death, myocardial infarction, stroke, acute liver injury, acute kidney injury, and thromboembolic events) up to 28 days postoperatively; and 3) the duration of mechanical ventilation, the length of intensive care unit (ICU) admission, and total duration of hospitalization, all censored at 28 days postoperatively.

The duration of the treatment period is 24 hours (from termination of CPB), and the duration of the study for each individual patient is 28 days.

Sample size

The sample size for this study was calculated based on the primary objective of demonstrating efficacy non-inferiority of the intervention (fibrinogen concentrate) relative to an active control (cryoprecipitate), with respect to the primary outcome. Determination of non-inferiority is based on a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of $\delta = 0.20$ around the mean units transfused. The choice of non-inferiority margin was largely motivated by the large degree of variation in utilization of blood products that is to be expected from previous studies reflecting current clinical practice, and clinical relevance in this setting.[24]

An empirical distribution function with a mean of 16 units and standard deviation of 14 units was calculated based on data from a previous study by Karkouti *et al*.[24] This was used to estimate study power by performing 10,000 simulations for each of the different possible sample sizes. Using this approach, we calculated an empirical power >90% with a sample

size ≥550 patients in each treatment group. Therefore, and assuming a 10% drop-out rate (patients randomized but not treated, or lost to-follow-up) for the study based on the use of two treatments that are within the standard-of-care for CPB surgery, the planned total sample size is 1,200 patients (600 per treatment group).

Randomization and blinding

The randomization schedule will be prepared by an independent biostatistician not involved in the conduct of the study using a permuted-block, random allocation schedule (stratified by study site). The random allocation schedule will be provided to participating centres in opaque, consecutively numbered envelopes and neither healthcare providers nor individuals responsible for randomizing patients will be aware of the treatment allocation at the time fibrinogen supplementation is ordered.

Patients will be randomized in a ratio of 1:1 to either the intervention (fibrinogen concentrate) group or the active control (cryoprecipitate) by the blood bank technologist once the order for fibrinogen supplementation is received and inclusion/exclusion criteria are confirmed. The requirement for informed consent prior to randomization will be waived (see Ethics section). Patients and outcome assessors will be blinded to treatment allocation throughout the study; clinicians will remain blinded only up to the point of use since the study products have distinct physical appearances and maintaining blinding is not logistically possible.

Data analysis plan

Data collection and management

Data collection will occur following randomization and procurement of consent (see Ethics section). Full details of the data to be collected during the study, together with the timing and frequency of data collection, are provided in ***Table 1***.

Table 1. Flow chart of study procedures and assessments performed at each study visit.

Procedures	Prior to Enrollment	Visit 1 Post-randomization (0–24 h)	Visit 1a 0–36 h Any additional IMP	Visit 2 POD7/DC	Visit 3 POD28
Blood bank receives fibrinogen order[a]	**X**	**(X)**[e]			
Inclusion and exclusion criteria	**X**				
Randomization	**X**				
IMP administration[b]		**X**			
Confirm integrated consent	**X**				
Obtain delayed consent		**X**	**(X)**	**(X)**	
Baseline data					
Demographics		**X**			
Medical history		**X**			
Preoperative medications		**X**			
Surgical data					
Intraoperative medications		**X**			
CPB time		**X**			
Cross-clamp time		**X**			
Circulatory arrest		**X**			
Vital signs		**X**			
Fluid in- and output monitoring		**X**			
Inotropes and vasopressors		**X**	**X**		

Procedures	Prior to Enrollment	Visit 1 Post-randomization (0–24 h)	Visit 1a 0–36 h Any additional IMP	Visit 2 POD7/DC	Visit 3 POD28
Laboratory assessments					
Chemistry[c]		**X**	**X**	**X**	
Hematology[c]		**X**[f]	**X**	**X**	
Coagulation profile[c]		**X**[f]	**X**	**X**	
Safety labs[c]		**X**	**X**	**X**	
Transfusion requirements[d]					
RBCs		**X**	**X**	**X**	
Pooled and apheresis platelets		**X**	**X**	**X**	
Plasma		**X**	**X**	**X**	
Other hemostatic products		**X**	**X**	**X**	
Blood loss determination using UDPB		**X**	**X**	**X**	
Extubation time		**X**	**(X)**	**(X)**	**(X)**
ICU length of stay		**X**	**(X)**	**(X)**	**(X)**
Hospital length of stay				**X**	**(X)**
AEs and SAEs		**X**	**X**	**X**	**X**
Concomitant medications		**X**	**X**	**X**	**X**
Physical examination		**X**	**X**		

[a] After the start of surgery and during or after CPB

[b] IMP will first be administered after the start of surgery based on the physician's judgment. The first IMP dose can be administered before fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives, *e.g.*, ROTEM® assay FIBTEM A10 of <12 mm, if available).

[c] As per standard practice.

[d] 24 hours after IMP administration.

[e] Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

[f] Prior to and 60 minutes after IMP administration.

( ) if needed.

Abbreviations: AE, adverse event; CPB, cardiopulmonary bypass; DC, discharge; ICU, intensive care unit; IMP, investigational medicinal product; POD, postoperative day; RBC, red blood cell; SAE, serious adverse event; UDPB, universal definition of perioperative bleeding.

All source records and source data will be maintained by the site investigator and preserved as stipulated by the regulatory authorities. An Electronic Data Capture (EDC) system will be used to collect study data. All patient information and data will be maintained as confidential, and patients will only be identified using a sequential numbering system. The site investigator will maintain a confidential patient identification code list.

Statistical methods

In this randomized, active control, non-inferiority trial, statistical analysis of the primary efficacy outcome will be conducted according to modified intention-to-treat (ITT) principles. The ITT population will comprise all randomized eligible patients who receive at least one dose of the allocated treatment and provide informed consent (see Ethics section). A secondary analysis will also be performed for the per-protocol (PP) population, which excludes patients with major protocol deviations (for example, receiving the incorrect treatment, receiving <80% of the planned dose, or missing the primary efficacy assessment).

To demonstrate that treatment with fibrinogen concentrate (intervention) is clinically non-inferior to cryoprecipitate (active control) with respect to the primary outcome, a two-sample, one-sided test of the hypotheses: H_0: $\mu F/\mu c \geq (1 + \delta)$ (inferiority), and H_1: $\mu F/\mu c < (1 + \delta)$ (non-inferiority), will be conducted (where μF and μc denote the mean number of transfused units in the fibrinogen concentrate and cryoprecipitate treatment groups, respectively). This will be based on a Poisson regression model and performed using a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$ around the mean units transfused. Non-inferiority of fibrinogen concentrate will be concluded if the upper limit of the one-sided confidence interval (CI) for the ratio $\mu F/\mu c$ is less than $(1 + \delta)$. Where non-inferiority is demonstrated, a test for clinical superiority of fibrinogen concentrate with respect to the number of ABPs transfused will be performed.

We also plan to examine a number of exploratory secondary outcomes in the analysis of efficacy: the number of ABPs administered from beginning of surgery up to 7 days postoperatively and within 24 hours after CPB termination, stratified by ABP type, will be examined using point estimates with two-sided 95% CIs, and descriptive statistics; major bleeding type will be evaluated by frequency distributions; and change in fibrinogen levels within 60 minutes before and after intervention will be tested using the Wilcoxon rank-sum test, and the Hodges-Lehmann estimator of median differences with 95% CIs. Analyses for efficacy will also be performed in patient subgroups, classified based on urgency and complexity of surgery.

Evaluation of safety outcomes, AEs, and SAEs will be conducted in the safety analysis population (SAF), comprising all patients who receive at least one dose of study drug and provide informed consent (see Ethics section). Analysis of AEs will focus on treatment

emergent adverse events (TEAEs), defined as AEs that start or worsen after the start of treatment (intervention or active control group). This analysis will be based on calculating point estimates and two-sided 95% CIs, in addition to descriptive statistics.

A pre-planned interim analysis will be conducted after 600 patients have completed the study. This will take the form of an unblinded interim analysis using an adjusted type I error rate according to the O'Brien-Fleming method.[25] At this point, enrollment may be stopped if a positive outcome, *i.e.*, rejection of H_0, is demonstrated (efficacy stop), or if the predictive power to test non-inferiority is insufficient (futility stop) (***Figure 2***). The study will continue as planned if neither scenario is fulfilled at the interim analysis.

Monitoring and quality control and assurance

An Independent Data and Safety Monitoring Committee (IDSMC) will be established by the Sponsor to review study data after each (approximately) 100 patients have been randomized. A meeting will also be convened to specifically evaluate the outcome of the pre-planned interim analysis. Meetings of the committee may also be called at other times, as deemed necessary based on occurrence of serious adverse events or any logistical concerns. The results of each IDSMC meeting will be communicated to the Principal Investigator and study Sponsor within 15 days, or earlier in matters relating to ensuring patient safety and/or study integrity. The IDSMC will comprise a minimum of three voting members with collective expertise in the fields of statistics, perioperative medicine, and hematology, who will review accumulating data pertaining to efficacy, safety, outcomes, and other study aspects such as recruitment, compliance, data quality, and risk versus benefit. The IDSMC will provide recommendations regarding the continuation, modification, or termination of the study, as appropriate. The duties and responsibilities of the IDSMC will be defined in a written, study-specific charter. Ultimately, the role of the IDSMC will be to protect and serve study participants, and to assist and advise the Principal Investigator and study Sponsor in the overall conduct, interpretation, validity, integrity, and ongoing relevance of the study.

For quality control and assurance purposes, periodic monitoring of all study-related source data/records, adherence to the approved study protocol, and the completeness and accuracy of CRFs will be undertaken by an appointed independent study monitor. Full and direct access to all source documents will be provided. All study-related material will also be made available to independent quality assurance auditors and regulatory inspectors, as required.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the ethical principles defined by the Declaration of Helsinki, and in compliance with the approved study protocol, Good Clinical Practice (GCP) guidelines, and all appropriate regulatory requirements governing the study

centres participating in the trial. The study, study protocol, and all other study documents have been approved by the local research ethics board (REB) and regulatory authority.

Due to the emergency nature of the clinical setting, *i.e.*, bleeding during or after surgery, all patients included in the study will be incapable of providing informed consent at the time treatment is required. Furthermore, delays brought about by obtaining surrogate consent can be severely detrimental to patient well-being. Moreover, this bleeding complication occurs infrequently (approximately 5% of cases) and cannot be reliably predicted before surgery, and a requirement to obtain prior consent from patients would make it impracticable to conduct the study. The study compares two fibrinogen replacement sources that are currently within the standard-of-care for this surgical procedure in patients who have consented to receiving blood transfusions, requires no additional interventions outside of standard clinical care, and therefore poses only minimal risk to patients. For the reasons outlined, the study therefore meets the criteria stated in Article 3.7A of the 2014 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans that define situations where exceptions to obtaining prior consent are warranted. As per these criteria, written informed consent from the patient (or a surrogate decision maker) for follow-up and use of their data will be obtained as soon as possible after randomization. Waiver of patient consent at time of randomization allows efficient inclusion of a large number of bleeding patients; this is a novelty of the study design and an approach not used before in bleeding surgical patients.

The trial has started recruitment and is registered on the ClinicalTrials.gov registry with the identifier NCT03037424. At completion of the study, and in accordance with the relevant guidelines, the Sponsor/Investigator will prepare a clinical study report (CSR) to report the outcomes of the study, and may publish the data in their entirety as a multi-centre dataset. We intend to disseminate the findings of the study in a timely fashion at international scientific meetings, and will publish our findings in the scientific/medical literature.

CONCLUSION

This protocol for the phase 3 FIBRES trial describes a multi-centre, randomized, non-inferiority study comparing the use of fibrinogen concentrate versus cryoprecipitate as active control in the treatment of acquired hypofibrinogenemia in patients undergoing CPB cardiac surgery. The study has a number of strengths. First, it utilizes a pragmatic approach and treatment algorithm that aligns with standard clinical practice. This not only increases the likelihood of protocol adherence, but also increases generalizability by ensuring that the study has direct clinical relevance to current treatment practice. Second, the waiver of patient consent prior to treatment improves study feasibility (cost and time) and minimizes post-randomization drop-outs. Third, use of an active control group ensures that all randomized patients receive fibrinogen supplementation according to clinical need. Fourth, the enrollment of approximately 1,200 patients represents the largest randomized controlled trial in this

setting to date.

This study in bleeding cardiac surgical patients aims to show efficacy non-inferiority of fibrinogen concentrate, a highly-purified fibrinogen product that has improved safety, ease of administration, and a predictable and robust effect on fibrinogen levels, when compared with cryoprecipitate. A finding of non-inferiority would support the use of this purified fibrinogen concentrate as an appropriate option for fibrinogen supplementation in acquired hypofibrinogenemia. Ultimately, the results of this trial are likely to improve the care of cardiac surgical patients experiencing significant bleeding, an under-studied yet high-risk population.

ACKNOWLEDGEMENTS

Editorial assistance was provided by Portland Medical Communications Ltd.

AUTHOR CONTRIBUTIONS

Conception and design (KK, JK); Preparation of the first draft of the manuscript (KK); Critical revision of the manuscript for important intellectual content (KK, JC, VR, NH, MF, MC, DS); Read and approved the final version of the manuscript to be published (KK, JC, VR, NH, MF, MC, DS).

FUNDING

This work was supported by Octapharma AG through an unrestricted grant for study conduct and the provision of fibrinogen concentrate. Cryoprecipitate was provided by Canadian Blood Services.

COMPETING INTERESTS

K Karkouti has received support for research and/or honoraria from Octapharma. Jeannie Callum has received support for research through peer-reviewed grants from Canadian Blood Services. Nancy Heddle is the Research Director for the McMaster Centre for Transfusion Research, which receives funding support from Canadian Blood Services and Health Canada.

The remaining authors have no competing interests or conflicts to declare.

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FIGURE LEGENDS

Figure 1. Study design.

Abbreviations: CPB, cardiopulmonary bypass.

Figure 2. Study decision process at the point of the interim analysis.

Abbreviations: IDSMC, Independent Data and Safety Monitoring Committee; N, number; PI, Principal Investigator.

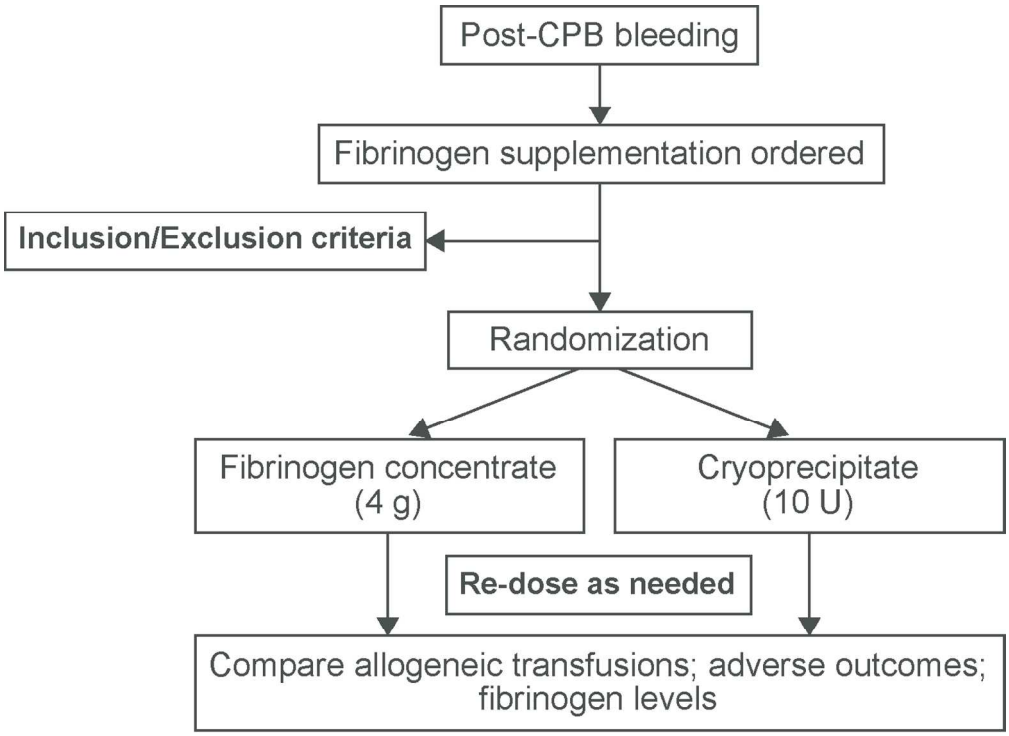

Figure 1. Study design.
Abbreviations: CPB, cardiopulmonary bypass.

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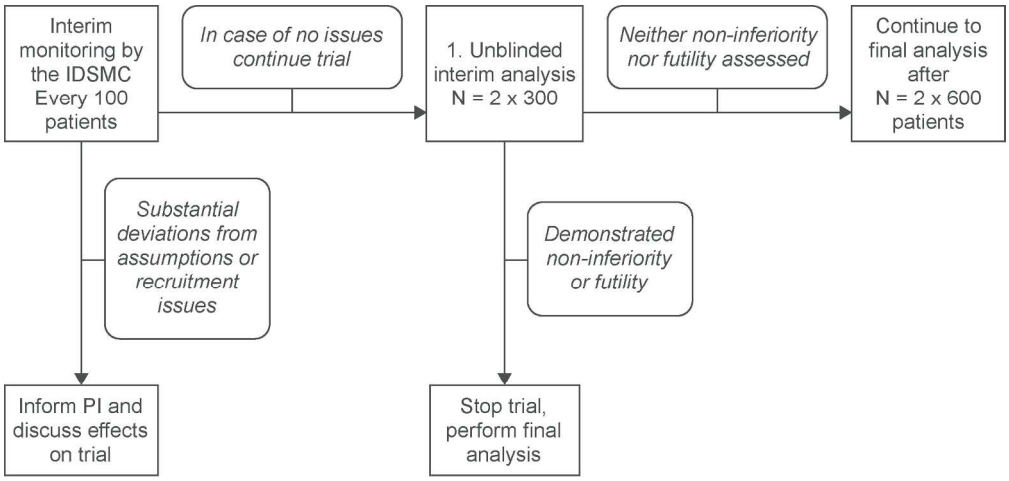

Figure 2. Study decision process at the point of the interim analysis.
Abbreviations: IDSMC, Independent Data and Safety Monitoring Committee; N, number; PI, Principal Investigator.

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020741.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Feb-2018
Complete List of Authors:	Karkouti, K; University of Toronto, Anesthesia Callum, Jeannie; Sunnybrook Health Sciences Centre, Clinical Pathology Rao, Vivek; University of Toronto, Surgery heddle, nancy; mcmaster university, faculty of health sciences Farkouh, Michael; University of Toronto, Medicine Crowther, Mark; McMaster University, Canada Scales, Damon; University of Toronto, Department of Critical Care
Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Cardiac surgery < SURGERY, Clinical trials < THERAPEUTICS, Blood bank & transfusion medicine < HAEMATOLOGY, HAEMATOLOGY

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

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Word count: 3,410

Keywords: Bleeding disorders and coagulopathies; Cardiac surgery; Clinical trials; Adult surgery; Blood bank & transfusion medicine; Haematology

ABSTRACT

Introduction: Coagulopathic bleeding is a serious complication of cardiac surgery to which an important contributor is acquired hypofibrinogenemia (plasma fibrinogen <1.5–2.0 g/L). The standard intervention for acquired hypofibrinogenemia is cryoprecipitate, but purified fibrinogen concentrates are also available. There is little comparative data between the two therapies and randomized trials are needed.

Methods and analysis: FIBrinogen REplenishment in Surgery (FIBRES) is a multi-center, randomized (1:1), active-control, single-blinded, phase 3 trial in adult cardiac surgical patients experiencing clinically significant bleeding related to acquired hypofibrinogenemia. The primary objective is to demonstrate that fibrinogen concentrate (Octafibrin/Fibryga, Octapharma) is non-inferior to cryoprecipitate. All patients for whom fibrinogen supplementation is ordered by the clinical team within 24 hours of cardiopulmonary bypass will receive 4 g fibrinogen concentrate or 10 units of cryoprecipitate (dose-equivalent to 4 g), based on random allocation and deferred consent. The primary outcome is total red cell, platelet, and plasma transfusions administered within 24 hours of bypass. Secondary outcomes include major bleeding, fibrinogen levels, and adverse events within 28 days. Enrollment of 1,200 patients will provide >90% power to demonstrate non-inferiority. One pre-planned interim analysis will include 600 patients. The pragmatic design and treatment algorithm align with standard practice, aiding adherence and generalizability.

Ethics and dissemination: The study is approved by the local research ethics board and will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and regulatory requirements. Patient consent prior to treatment is waived, as per criteria in the Tri-Council Policy Statement. Results will be published in the scientific/medical literature, and at international congresses. Non-inferiority of purified fibrinogen concentrate would support its use in acquired hypofibrinogenemia. The results are likely to improve care for cardiac surgical patients experiencing significant bleeding, an under-studied yet high-risk population.

Trial registration: NCT03037424 (ClinicalTrials.gov).

Word count: 294 (max. 300 words)

STRENGTHS AND LIMITATIONS OF THIS STUDY

[Up to 5 bullets, no longer than one sentence each, each relating to the methods]

- This is the largest randomized comparison of fibrinogen concentrate versus cryoprecipitate in adult patients with acquired hypofibrinogenemia due to cardiac surgery involving cardiopulmonary bypass.
- Simple, pragmatic study design that aligns with standard clinical practice will enhance adherence and ensure clinical relevance and generalizability, while stratified randomization by study site is employed to address between-site practice variability.
- Use of an active control, cryoprecipitate, as the comparator guarantees that all patients in the study will receive fibrinogen supplementation as clinically indicated.
- The large sample size of approximately 1,200 patients in this high-risk population will provide >90% power to detect non-inferiority of fibrinogen concentrate to cryoprecipitate.
- It will not be possible to fully blind clinicians to treatment allocation, so all outcome assessors will be blinded to minimize the risk of bias.

INTRODUCTION

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in approximately 10% or more of cases, it often requires massive blood transfusion with allogeneic blood products (ABPs), and is associated with an increased risk of serious postoperative adverse outcomes, including sepsis, renal failure, and death.[1-4] While the causes of coagulopathy in this setting are likely to be multifactorial, acquired hypofibrinogenemia, considered as a deficiency in plasma fibrinogen levels below 1.5–2.0 g/L,[5] is believed to be one of the primary factors.[6]

Fibrinogen is the most abundant clotting factor in the human circulation and plays a pivotal role in hemostasis and the coagulation cascade by promoting clot formation and platelet aggregation.[7] Physiological levels of fibrinogen are typically in the range of 1.5–4.5 g/L,[8] with a half-life following synthesis of approximately four days.[9] A number of factors may contribute to the development of acquired hypofibrinogenemia in cardiac surgery. Fibrinogen loss may result from acute bleeding, dilution of the circulatory volume due to administration of fluids and priming of the CPB circuit, and consumption due to activation of the coagulation cascade during CPB.[10] Since fibrinogen has only a limited reserve in the body, a modest decrease in levels to <1.5–2.0 g/L impairs coagulation and increases the likelihood of bleeding complications.[10-15] Fibrinogen levels have been shown to fall 40–50% during cardiac surgery,[10] with a critical drop observed in approximately 5% of patients.[16] In these patients, fibrinogen supplementation is believed to be essential and is the current standard of care in most jurisdictions.[6,17]

While supplementation of fibrinogen has historically included the use of fresh frozen plasma, the two principal options currently recommended for supplementation in acquired hypofibrinogenemia are cryoprecipitate and purified fibrinogen concentrate.[5] Cryoprecipitate is currently used in North America and is an ABP prepared from fresh frozen plasma through a process of thawing and centrifugation. The clotting factor-enriched precipitate is re-suspended in a small volume of plasma and refrozen. Typical fibrinogen content is around 15 g/L,[18] although this may vary considerably (3–30 g/L) due to inter-donor variability.[19] Cryoprecipitate has largely been withdrawn from most European countries due to safety concerns because it does not undergo pathogen reduction,[20] where treatment with purified human fibrinogen concentrate is the preferred therapeutic choice for hypofibrinogenemia. Fibrinogen concentrate has a number of important advantages over cryoprecipitate, including: significantly higher purity; standardized fibrinogen content, enabling more accurate dosing; faster preparation and administration time; no requirement for blood type matching; and improved safety, particularly through pathogen reduction technology.[6,20-22] Cryoprecipitate remains the most common fibrinogen replacement product in North America and may be a more effective hemostatic agent because it also contains hemostatic factors VIII and XIII, von Willebrand factor, and platelet microparticles.

There is scant data comparing cryoprecipitate and fibrinogen concentrate for the treatment of acquired hypofibrinogenemia; thus, we do not know which of these is the most appropriate therapy in bleeding cardiac surgical patients. Moreover, mounting evidence indicates that hemostatic management of patients with coagulopathic bleeding is evolving from the conventional use of non-purified ABPs to targeted therapeutic algorithms using purified coagulation factor concentrates such as fibrinogen concentrate.[23] There is therefore a need for prospective, randomized clinical trials designed to specifically evaluate cryoprecipitate and fibrinogen concentrate in parallel as part of hemostatic treatment algorithms in bleeding cardiac surgical patients.

Our study design addresses these issues by assessing non-inferiority of a purified fibrinogen concentrate against cryoprecipitate for the treatment of acquired hypofibrinogenemia in cardiac surgery. Given the theoretical and logistical advantages of fibrinogen concentrate relative to cryoprecipitate outlined above, illustrating that fibrinogen concentrate is non-inferior to cryoprecipitate would support the use of this purified fibrinogen concentrate for hemostatic management in this high-risk, clinically important setting. Importantly, the conduct of randomized trials in bleeding surgical patients poses specific challenges, and this trial incorporates several design features to address these challenges.

METHODS AND ANALYSIS

Objective

The primary objective of this study is to demonstrate that the administration of the fibrinogen concentrate Octafibrin/Fibryga (Octapharma AG, Lachen, Switzerland; currently approved in Canada for the treatment of congenital afibrinogenemia and hypofibrinogenemia) is non-inferior to cryoprecipitate for treating bleeding in cardiac surgical patients in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards.

Study design and setting

The FIBrinogen REplenishment in Surgery (FIBRES) trial is a pragmatic, multi-center, randomized, active-control, non-inferiority phase 3 trial in adult cardiac surgical patients experiencing clinically significant bleeding in whom fibrinogen supplementation is deemed to be necessary. A pragmatic study design was chosen because it allows participating sites and surgical teams to maintain standard clinical practice when treating patients, making the study clinically relevant and generalizable to the large population of patients undergoing cardiac surgery, and increases the likelihood of protocol adherence and successful study completion. Approximately 1,200 patients will be recruited from up to 12 Canadian hospitals. Patients will be randomized when fibrinogen supplementation is ordered to either of two treatment groups: fibrinogen concentrate 4 g (intervention) or cryoprecipitate 10 units (active control). No placebo arm has been included in the trial because withholding effective treatment is neither

consistent with standard practice nor acceptable on ethical grounds. Treatment arm allocation will be maintained for up to 24 hours after termination of CPB; only the randomly-allocated fibrinogen replacement product can be provided during this time. No other aspects of care will be modified. Informed consent will be obtained from patient or surrogate decision maker as soon as possible after surgery. An overview of the study design is presented in ***Figure 1***. The study commenced in February 2017 and is expected to complete in late 2018, with results available in early 2019.

Eligibility criteria

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). The exclusion criteria are: receipt of either fibrinogen concentrate or cryoprecipitate within 24 hours before surgery; a history of severe allergic reaction to fibrinogen concentrate or cryoprecipitate; known refusal of ABPs or either study treatment (*i.e.*, for religious reasons); a known fibrinogen level >3.0 g/L within 30 minutes of the order for treatment (to eliminate the risk of raising a patient's fibrinogen level above the upper limit of the normal range [4.0 g/L]); and known pregnancy.

Interventions

Intervention

Patients randomized to the intervention group will receive fibrinogen concentrate administered by slow (over 10 minutes) intravenous injection immediately after reconstitution with 50 mL of sterile water for injection, as per the manufacturer's instructions. Patients randomized to this group will receive 4 g of fibrinogen concentrate each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB surgery.

Active control

Those patients randomized to the active control group will each receive cryoprecipitate, given as 10 units (dose-equivalent to approximately 4 g [median 388 mg, range 120–796 mg, per bag], as per internal Canadian Blood Services quality control data; personal communication, Canadian Blood Services [24]) each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB. Cryoprecipitate will be prepared according to current Health Canada standards and administered by intravenous infusion following hospital transfusion policies at each of the participating study sites.

In both study arms, study treatment (fibrinogen concentrate or cryoprecipitate) may be administered prior to the determination of fibrinogen levels in a patient that is bleeding if deemed appropriate as per current clinical standards (*i.e.*, rapid bleeding precluding waiting for laboratory results). If fibrinogen supplementation is needed after the 24-hour study period

is over, patients will receive cryoprecipitate, which is the current standard-of-care in most of Canada. Concomitant medications to treat bleeding that are part of standard patient care will be permitted throughout the study, but must be recorded in the case report form (CRF).

Outcomes and study duration

The primary outcome of the study is one of efficacy; specifically, comparison between study groups of the total number of red cells, platelets, and plasma administered during the first 24 hours after termination of CPB surgery.

Secondary outcomes of the study will include both efficacy and safety outcomes. For the former, the secondary outcomes are: 1) comparison of the total number of ABPs (not including cryoprecipitate) administered from the start of surgery up to seven days after surgery (or discharge if earlier); 2) comparison of major bleeding (using the modified universal definition of perioperative bleeding [UDPB] in cardiac surgery)[25] during the first 24 hours after termination of CPB; and 3) comparison of the effect of treatment on plasma fibrinogen levels, determined by the change from within 75 minutes before to 75 minutes after completion of the first dose of fibrinogen supplementation. The secondary safety outcomes are: 1) adverse events (AEs) and serious AEs (SAEs) up to 28 days postoperatively; 2) a composite AE grouping (death, myocardial infarction, stroke, acute liver injury, acute kidney injury, and thromboembolic events) up to 28 days postoperatively; and 3) the duration of mechanical ventilation, the length of intensive care unit (ICU) admission, and total duration of hospitalization, all censored at 28 days postoperatively.

The duration of the treatment period is 24 hours (from termination of CPB), and the duration of the study for each individual patient is 28 days.

Sample size

The sample size for this study was calculated based on the primary objective of demonstrating efficacy non-inferiority of the intervention (fibrinogen concentrate) relative to an active control (cryoprecipitate), with respect to the primary outcome. Determination of non-inferiority is based on a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of $\delta = 0.20$ around the mean units transfused. The choice of non-inferiority margin was largely motivated by the large degree of variation in utilization of blood products that is to be expected from previous studies reflecting current clinical practice, and clinical relevance in this setting.[26]

An empirical distribution function with a mean of 16 units and standard deviation of 14 units was calculated based on data from a previous study by Karkouti *et al* (each dose of apheresis or pooled platelets was counted as 4 units to correspond with the number of units in pooled platelets).[26] This was used to estimate study power by performing 10,000 simulations for

each of the different possible sample sizes. Using this approach, we calculated an empirical power >90% with a sample size ≥550 patients in each treatment group. Therefore, and assuming a 10% drop-out rate (patients randomized but not treated, or lost to-follow-up) for the study based on the use of two treatments that are within the standard-of-care for CPB surgery, the planned total sample size is 1,200 patients (600 per treatment group).

Randomization and blinding

The randomization schedule will be prepared by an independent biostatistician not involved in the conduct of the study using a permuted-block, random allocation schedule. As transfusion practice is not standardized, randomization will be stratified by study site. The random allocation schedule will be provided to participating centers in opaque, consecutively numbered envelopes and neither healthcare providers nor individuals responsible for randomizing patients will be aware of the treatment allocation at the time fibrinogen supplementation is ordered.

Patients will be randomized in a ratio of 1:1 to either the intervention (fibrinogen concentrate) group or the active control (cryoprecipitate) by the blood bank technologist once the order for fibrinogen supplementation is received and inclusion/exclusion criteria are confirmed. The requirement for informed consent prior to randomization will be waived (see Ethics section). Patients will be blinded to treatment allocation throughout the study; treating clinicians will remain blinded only up to the point of use since the study products have distinct physical appearances and maintaining blinding is not logistically possible. All attempts will be made to blind clinicians outside of the operating room and ICU, as well as outcome assessors, to the treatment allocation.

Data analysis plan

Data collection and management

Data collection will occur following randomization and procurement of consent (see Ethics section). Full details of the data to be collected during the study, together with the timing and frequency of data collection, are provided in ***Table 1***.

Table 1. Flow chart of study procedures and assessments performed at each study visit.

Procedures	**Prior to Enrollment**	**Visit 1** Post-randomization (0–24 h)*	**Visit 2** POD7/DC	**Visit 3** POD28
Blood bank receives fibrinogen order[a]	**X**	**(X)**[e]		
Inclusion and exclusion criteria	**X**			
Randomization	**X**			
IMP administration[b]		**X**		
Patient (surrogate) debriefing and consent	**X**			
Obtain delayed consent		**X**	**(X)**	
Baseline data				
Demographics		**X**		
Medical history		**X**		
Preoperative medications		**X**		
Surgical data				
Intraoperative medications		**X**		
CPB time		**X**		
Cross-clamp time		**X**		
Circulatory arrest		**X**		
Vital signs		**X**		
Fluid in- and output monitoring		**X**		

Procedures	Prior to Enrollment	Visit 1 Post-randomization (0–24 h)*	Visit 2 POD7/DC	Visit 3 POD28
Inotropes and vasopressors		X		
Laboratory assessments				
Chemistry[c]		X	X	
Hematology[c]		X[f]	X	
Coagulation profile[c]		X[f]	X	
Safety labs[c]		X	X	
Transfusion requirements[d]				
RBCs		X	X	
Pooled and apheresis Platelets		X	X	
Plasma		X	X	
Other hemostatic products		X	X	
Blood loss determination using UDPB		X	X	
Extubation time		X	(X)	(X)
ICU length of stay		X	(X)	(X)
Hospital length of stay			X	(X)
AEs and SAEs		X	X	X
Concomitant medications		X	X	X
Physical examination		X		

* For any activities not completed during this visit, additional visits will be undertaken to complete activities

[a] After the start of surgery and during or after CPB

[b] IMP will first be administered after CPB termination

[c] As per standard practice.

[d] From beginning of surgery to postoperative day 7.

[e] Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period (up to 24 hours after termination of CPB).

[f] Prior to and up to 75 minutes after IMP administration.

( ) if needed.

Abbreviations: AE, adverse event; CPB, cardiopulmonary bypass; DC, discharge; ICU, intensive care unit; IMP, investigational medicinal product; POD, postoperative day; RBC, red blood cell; SAE, serious adverse event; UDPB, universal definition of perioperative bleeding.

All source records and source data will be maintained by the site investigator and preserved as stipulated by the regulatory authorities. An Electronic Data Capture (EDC) system will be used to collect study data. All patient information and data will be maintained as confidential, and patients will only be identified using a sequential numbering system. The site investigator will maintain a confidential patient identification code list.

Statistical methods

In this randomized, active control, non-inferiority trial, statistical analysis of the primary efficacy outcome will be conducted according to modified intention-to-treat (ITT) principles. The mITT population will comprise all randomized eligible patients who undergo cardiac surgery, receive at least one (partial or complete) dose of the allocated treatment and for whom consent was obtained (see Ethics section). A secondary analysis will also be performed for the per-protocol (PP) population, which excludes patients with major protocol deviations (for example, receiving the incorrect treatment, receiving <80% of the planned dose, or missing the primary efficacy assessment).

To demonstrate that treatment with fibrinogen concentrate (intervention) is clinically non-inferior to cryoprecipitate (active control) with respect to the primary outcome, a two-sample, one-sided test of the hypotheses: H_0: $\mu F/\mu c \geq (1 + \delta)$ (inferiority), and H_1: $\mu F/\mu c < (1 + \delta)$ (non-inferiority), will be conducted (where μF and μc denote the mean number of transfused units in the fibrinogen concentrate and cryoprecipitate treatment groups, respectively). This will be based on a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term [27]) and clinical non-inferiority margin of $\delta = 0.20$ around the mean units transfused. Non-inferiority of fibrinogen concentrate will be concluded if the upper limit of the one-sided confidence interval (CI) for the ratio $\mu F/\mu c$ is less than $(1 + \delta)$. Where non-inferiority is demonstrated, a test for clinical superiority of fibrinogen concentrate with respect to the number of ABPs transfused will be performed by testing the hypotheses: H'_0: $\mu F/\mu c \geq 1$ (inferiority), and H'_1: $\mu F/\mu c < 1$ (superiority),

We also plan to examine a number of exploratory secondary outcomes in the analysis of efficacy: the number of ABPs administered from beginning of surgery up to 7 days postoperatively and within 24 hours after CPB termination, stratified by ABP type, will be examined using point estimates with two-sided 95% CIs, and descriptive statistics; major bleeding type will be evaluated by frequency distributions; and change in fibrinogen levels within 60 minutes before and after intervention will be tested using the Wilcoxon rank-sum test, and the Hodges-Lehmann estimator of median differences with 95% CIs. Analyses for efficacy will also be performed in patient subgroups, classified based on urgency and complexity of surgery.

Evaluation of safety outcomes, AEs, and SAEs will be conducted in the safety analysis

population (SAF), comprising all patients who receive at least one dose of study drug and provide informed consent (see Ethics section). Analysis of AEs will focus on treatment emergent adverse events (TEAEs), defined as AEs that start or worsen after the start of treatment (intervention or active control group). This analysis will be based on calculating point estimates and two-sided 95% CIs, in addition to descriptive statistics.

The number of patients who died will be summarized. A possible difference between treatment groups will be estimated by the risk ratio with 95% CI. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented.

One pre-planned interim analysis will be conducted after 600 patients have been randomized. This will take the form of an unblinded interim analysis using an adjusted type I error rate according to the O'Brien-Fleming method.[28] At this point, enrollment may be stopped if a positive outcome, *i.e.*, rejection of H_0, is demonstrated based on the adjusted one-sided significance level of $\alpha = 0.00258$ (efficacy stop), or if the predictive power for the test of non-inferiority is less than 0.25 (futility stop) (***Figure 2***). The study will continue as planned if neither scenario is fulfilled at the interim analysis. A final analysis will then be performed after an additional 600 patients have been randomized at the adjusted significance level of $\alpha = 0.02242$ to maintain the overall one-sided significance level of 0.025.

Monitoring and quality control and assurance

An Independent Data and Safety Monitoring Committee (IDSMC) will be established by the Sponsor to review study data after each (approximately) 100 patients have been randomized. A meeting will also be convened to specifically evaluate the outcome of the pre-planned interim analysis. Meetings of the committee may also be called at other times, as deemed necessary based on occurrence of serious adverse events or any logistical concerns. The results of each IDSMC meeting will be communicated to the Principal Investigator and study Sponsor within 15 days, or earlier in matters relating to ensuring patient safety and/or study integrity. The IDSMC will comprise a minimum of three voting members with collective expertise in the fields of statistics, perioperative medicine, and hematology, who will review accumulating data pertaining to efficacy, safety, outcomes, and other study aspects such as recruitment, compliance, data quality, and risk versus benefit. The IDSMC will provide recommendations regarding the continuation, modification, or termination of the study, as appropriate. The duties and responsibilities of the IDSMC will be defined in a written, study-specific charter. Ultimately, the role of the IDSMC will be to protect and serve study participants, and to assist and advise the Principal Investigator and study Sponsor in the overall conduct, interpretation, validity, integrity, and ongoing relevance of the study. The sponsor will have ultimate authority in all aspects of the trial and will have access to the final trial dataset.

For quality control and assurance purposes, periodic monitoring of all study-related source data/records, adherence to the approved study protocol, and the completeness and accuracy of CRFs will be undertaken by an appointed independent study monitor. Full and direct access to all source documents will be provided. All study-related material will also be made available to independent quality assurance auditors and regulatory inspectors, as required.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the ethical principles defined by the Declaration of Helsinki, and in compliance with the approved study protocol, Good Clinical Practice (GCP) guidelines, and all appropriate regulatory requirements (including collecting and reporting of serious adverse events) governing the study centers participating in the trial. The study, study protocol, and all other study documents have been approved by the University Health Network's (the coordinating center) research ethics board (REB # 16-5636; Approval date: 12 Jan, 2017), the local REB of all participating sites, and regulatory authority (Health Canada). The trial is registered at clinicaltrials.gov (Identifier: NCT03037424). Changes to protocol will be communicated by the Sponsor to all REBs, Health Canada, and will be documented on clinicaltrials.gov.

Due to the emergency nature of the clinical setting, *i.e.*, bleeding during or after surgery, all patients included in the study will be incapable of providing informed consent at the time treatment is required. Furthermore, delays brought about by obtaining surrogate consent can be severely detrimental to patient well-being. Moreover, this bleeding complication occurs infrequently (approximately 5% of cases) and cannot be reliably predicted before surgery, and a requirement to obtain prior consent from patients would make it impracticable to conduct the study. The study compares two fibrinogen replacement sources that are currently within the standard-of-care for this surgical procedure in patients who have consented to receiving blood transfusions, requires no additional interventions outside of standard clinical care, and therefore poses only minimal risk to patients. For the reasons outlined, the study therefore meets the criteria stated in Article 3.7A of the 2014 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans that define situations where exceptions to obtaining prior consent are warranted. As per these criteria, 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. Waiver of patient consent at time of randomization allows efficient inclusion of a large number of bleeding patients and minimizes post-randomization drop-outs; this is a novelty of the study design and an approach not commonly used in bleeding surgical patients.

At completion of the study, and in accordance with the relevant guidelines, the Sponsor/Investigator will prepare a clinical study report (CSR) to report the outcomes of the study, and may publish the data in their entirety as a multi-center dataset. We intend to disseminate the findings of the study in a timely fashion at international scientific meetings, and will publish our findings in the scientific/medical literature.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involvement in the design of the study.

CONCLUSION

This protocol for the phase 3 FIBRES trial describes a multi-center, randomized, non-inferiority study comparing the use of fibrinogen concentrate versus cryoprecipitate as active control in the treatment of acquired hypofibrinogenemia in patients undergoing CPB cardiac surgery. The study has a number of strengths. First, it utilizes a pragmatic approach and treatment algorithm that aligns with standard clinical practice. This not only increases the likelihood of protocol adherence, but also increases generalizability by ensuring that the study has direct clinical relevance to current treatment practice. Second, the waiver of patient consent prior to treatment improves study feasibility (cost and time) and minimizes post-randomization drop-outs. Third, use of an active control group ensures that all randomized patients receive fibrinogen supplementation according to clinical need. Fourth, the enrollment of approximately 1,200 patients represents the largest randomized controlled trial in this setting to date.

This study in bleeding cardiac surgical patients aims to show efficacy non-inferiority of fibrinogen concentrate, a highly-purified fibrinogen product that has improved safety, ease of administration, and a predictable and robust effect on fibrinogen levels, when compared with cryoprecipitate. A finding of non-inferiority would support the use of this purified fibrinogen concentrate as an appropriate option for fibrinogen supplementation in acquired hypofibrinogenemia. Ultimately, the results of this trial are likely to improve the care of cardiac surgical patients experiencing significant bleeding, an under-studied yet high-risk population.

ACKNOWLEDGMENTS

Editorial assistance was provided by Portland Medical Communications Ltd.

AUTHOR CONTRIBUTIONS

Conception and design (KK, JC); Preparation of the first draft of the manuscript (KK); Critical revision of the manuscript for important intellectual content (KK, JC, VR, NH, MF, MC, DS); Read and approved the final version of the manuscript to be published (KK, JC, VR, NH, MF, MC, DS).

FUNDING

This work was supported by Octapharma AG through an unrestricted grant for study conduct and the provision of fibrinogen concentrate. Cryoprecipitate was provided by Canadian Blood Services.

COMPETING INTERESTS

K Karkouti has received support for research and/or honoraria from Octapharma. Jeannie Callum has received support for research through peer-reviewed grants from Canadian Blood Services. Nancy Heddle is the Research Director for the McMaster Centre for Transfusion Research, which receives funding support from Canadian Blood Services and Health Canada.

The remaining authors have no competing interests or conflicts to declare.

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FIGURE LEGENDS

Figure 1. Study design.

Abbreviations: CPB, cardiopulmonary bypass.

Figure 2. Study decision process at the point of the interim analysis.

Abbreviations: IDSMC, Independent Data and Safety Monitoring Committee; N, number; PI, Principal Investigator.

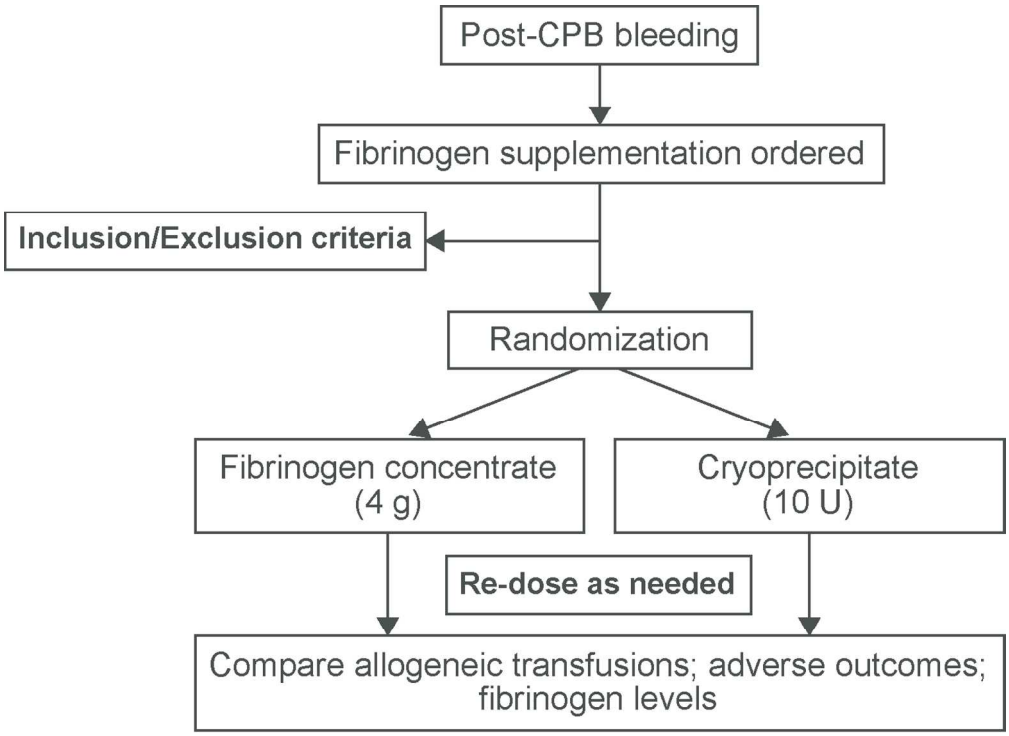

Figure 1. Study design.
Abbreviations: CPB, cardiopulmonary bypass.

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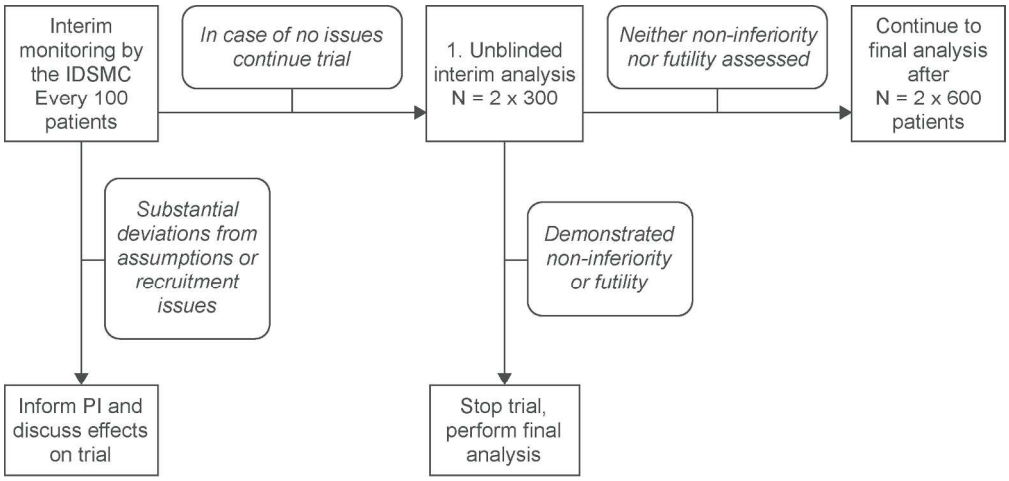

Figure 2. Study decision process at the point of the interim analysis.
Abbreviations: IDSMC, Independent Data and Safety Monitoring Committee; N, number; PI, Principal Investigator.

204x96mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 14
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	–
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	–
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7, 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8–12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13, 14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	–
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	–
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14, 15
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	–
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	–
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	–

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.