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Efficacy of prothrombin complex concentrate (PPC) versus fresh frozen plasma (FFP) in reducing perioperative blood loss in cardiac surgery: study protocol for a non-inferiority, randomized controlled trial

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ABSTRACT

Objective: To explore whether 4-factor prothrombin complex concentrate (PCC) is not inferior to Fresh frozen plasma (FFP) with regard to reducing perioperative blood loss in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB).

Setting: National Centre for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital in China.

Participants: Patients undergoing elective CABG, valve replacement or valvuloplasty under CPB, between 18 and 80 years old, will be included.

Design: This study is a non-inferiority, randomized controlled clinical trial. A total of 560 subjects will be randomly divided into 2 groups (group PCC and group FFP), with 280 patients in each group. Preoperative management, anaesthetic and surgical techniques will be standardized for both groups. When the activated partial thromboplastin time (APTT) is prolonged (>1.5-times normal),

patients will be given a 4-factor PCC based on patient body weight and the international normalized ratio (INR) in the PCC group and a dose of 10-15 ml/kg FFP in the FFP group.

Primary and Secondary Outcome Measures: The primary outcome is the volume of blood loss during and within 24 hours after surgery. The secondary outcomes include (1) the total units of allogeneic red blood cells (RBCs) transfused during and within 7 days after surgery and (2) re-exploration due to postoperative bleeding within 7 days after surgery.

Trial registration: Registered under NCT04244981 at ClinicalTrials.gov on 28 January 2020, https://clinicaltrials.gov/ct2/show/NCT04244981?cond=NCT04244981&draw=2&rank=1

Ethical approval: This study has been approved by the ethics committee of Peking Union Medical College Hospital (ZS-2242).

Key words: prothrombin complex concentrate, fresh frozen plasma, perioperative blood loss, cardiac surgery, cardiopulmonary bypass

Strengths and Limitations:

- This study focuses on the efficacy of prothrombin complex concentrate (PCC), compared with fresh frozen plasma (FFP), in reducing perioperative blood loss under cardiopulmonary bypass in cardiac surgery.
- Considering the insufficiency and disadvantages of FFP, such as long infusion times, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload, the study may provide an alternative strategy for the treatment of major blood loss in cardiac surgery.
- Multiple strategies will be put in place to mitigate the risk of sampling, undercoverage, recruitment and participation bias as well as measurement error.

BACKGROUND

Major bleeding and allogeneic blood transfusion are major complications of cardiac surgery[1,2] and can prolong mechanical ventilation time, cause acute respiratory distress syndrome (ARDS), sepsis, neurological complications[3], vasoparalysis[4] and arrhythmia[5,6], and increase the incidence of sternal infection[7], blood transfusion-related complications and surgical mortality[8]. In addition, these complications can also significantly increase medical costs[9].

Coagulopathy is one of the main reasons for massive perioperative bleeding and allogeneic blood transfusion in cardiac surgery and cardiopulmonary bypass (CPB)[10]. The causes of coagulopathy include excessive fibrinolysis, platelet dysfunction, and coagulation factor deficiency due to consumption and dilution[11-13]. High levels of coagulation factors are activated and consumed after CPB, which is one of the main causes of postoperative blood loss in cardiac surgery[14,15]. Fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) are currently used primarily to treat perioperative coagulopathy in cardiac surgery[16] and are deemed suitable for increasing the concentration of vitamin K-dependent coagulation factors. These two products contain factors II, VII, IX, and X and thus help restore normal levels of the clotting fraction[17,18].

FFP is human plasma frozen within a specific period after collection[19] and is always insufficient in clinical therapy. ABO typing and thawing are required before use, and FFP is associated with long infusion times. More importantly, FFP can be associated with severe adverse outcomes including transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload. PCC is derived from pooled, virus-inactivated human plasma products and offers a rapid method for replacing vitamin K-dependent clotting factors and restoring normal haemostasis in the context of over-anticoagulation. PCC can be prepared quicker than FFP and administered without warming. PCC administration also avoids the volume overload usually associated with FFP, reducing the incidence of blood transfusions and the risk of TRALI. In addition, PCC also has a better safety profile than FFP because of its viral inactivation, minimizing the risk of transmission of a variety of infective agents[20-22].

PCC can be divided into two types depending on whether FVII is included: 3-factor PCC and 4-factor PCC[23,24]. Three-factor PCC is mainly used for the treatment of primary coagulopathy, such as haemophilia B[25,26], and 4-factor PCC is used for the treatment of secondary coagulopathy, such as anticoagulant overdose and severe liver disease[27].

Some experience with the use of PCC to reverse warfarin anticoagulation in patients undergoing emergency cardiac surgery has been reported[28-30]. However, PCC has not been studied systematically for the treatment of perioperative blood loss during cardiac surgery and CPB. In this study, we will explore whether 4-factor PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB.

METHODS

Objective

This study aims to determine whether PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB.

Design

This is a non-inferiority, randomized controlled clinical trial. The trial will be conducted at the National Center for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital, China. A total of 560 participants will be randomized. The trial schema is shown in Figure 1, and the study period is shown in Figure 2.

Inclusion criteria

Eligible patients must meet all of the following criteria:

1. Age between 18 and 80 years.
2. Elective coronary artery bypass grafting (CABG) or valve replacement or valvuloplasty through CPB.
3. Signing of the informed consent form.

Exclusion criteria

The exclusion criteria are as follows:

1. History of cardiac surgery.

2. Hepatic dysfunction.
3. Renal insufficiency (serum creatinine higher than 176 μmol/l).
4. Severe coagulopathy.
5. Withdrawal of clopidogrel or aspirin less than 7 days and low molecular weight heparin less than 24 hours before surgery.
6. Haematological disorders.
7. Mass blood transfusion 24 hours before surgery.
8. Allergy to allogeneic blood products.
9. Pregnancy.
10. Other serious diseases that may affect patient survival time, such as tumours.

Randomization and blinding

Stratified randomization will be used to assign the patients to two groups (group PCC and FFP). After enrolment and 1 hour before the operation, the patients will be randomized by a specific computer randomization system based on the type of surgery (CABG or valve replacement/valvuloplasty). Anaesthesia nurses will prepare the corresponding products for each patient according to the group assignments in an anaesthesia preparation room. Participants, anaesthesiologists, surgeons, and outcome assessors will all be blinded to the group assignments throughout the trial. In the case of the need for emergency rescue, if it is necessary to know the intervention for a participant, blinding will be broken. The allocation will be disclosed to healthcare providers in case of emergency in compliance with ethics considerations.

Interventions

A total of 560 patients who meet the criteria will be randomly divided into 2 groups named the prothrombin complex concentrate group (group PCC) and the fresh frozen plasma group (control group and group FFP, respectively), with 280 cases in each group. Preoperative management and anaesthetic and surgical techniques will be standardized for all patients. Various demographic as well as preoperative physiological and laboratory parameters will be recorded for each patient. During the operation, all patients will be under general anaesthesia. The surgical procedures will be performed through a median sternotomy approach, and CPB will be undertaken in a standardized

fashion. A mild hypothermia condition (32-34℃) will be achieved, and heparin (400 IU/kg) will be intravenously administered before initiation of CPB, with activated clotting time (ACT) maintained above 480 seconds during CPB. In addition, tranexamic acid will be intravenously administered after the induction of anaesthesia until the end of the operation (20 mg/kg for the first hour and 2 mg/kg thereafter). After CPB, circulating heparin will be antagonized with protamine sulfate at a ratio of 1 mg of protamine per 100 IU of heparin. Prolonged ACT after surgery will be treated with an additional dose of protamine sulfate. The cell saver machine will be used during surgery, and the following parameters should be checked and corrected off bypass as necessary: (1) patient's core temperature, (2) arterial blood gases (ABGs), (3) post CPB coagulation screening results: a) the platelet count, b) the international normalized ratio (INR), c) the activated partial thromboplastin time (APTT) and prothrombin time (PT) and d) serum fibrinogen levels. Off bypass, all patients' core temperatures will be raised above 37℃. Generally, when visual inspection reveals microvascular bleeding or substantial blood collection in the cardiotomy reservoir (generally 200 ml after weaning from CPB), the patient will receive an assessment of the haemostasis/coagulation profile through thromboelastography (TEG).

A prolonged APTT (>1.5-times normal)[31] will be regarded as the initiator for administration of PCC or FFP according to the group assignments. In group PCC, patients will be given a 4-factor PCC (Confidex®, CSL Behring, Marburg, Germany) based on their body weights and INRs[32] (Table 1). In group FFP, patients will be given FFP based on their body weights (10-15 ml/kg). The APTT and INR will be re-evaluated half an hour after transfusion, and an additional dose will be administered if required. Other allogeneic blood products will be needed if cell saver is insufficient for patients, and transfusion will be guided by the haemoglobin concentration, TEG, the platelet count, the INR, the PT, the APTT and serum fibrinogen levels. Homologous red blood cells (RBCs) will be intraoperatively administered to maintain a haemoglobin concentration >7 g/dl or a haematocrit higher than 20%. Platelets will be transfused when their count is $\leq 60\times10^9$/l. Serum fibrinogen levels less than 1.5 g/l will be corrected with fibrinogen concentrate at doses of 25-50 mg/kg[31]. Additional blood

product transfusions will be performed at the discretion of the individual surgeon or attending anaesthesiologist.

After surgery, patients will be sent to the intensive care unit (ICU) and then back to the ward after their conditions stabilize. Patients' haemoglobin concentrations, haematocrit levels, platelet counts, INRs, PTs, APTTs, fibrinogen levels and blood biochemistry parameters will be monitored daily in the ICU. RBCs will be transfused if the haemoglobin concentration is ≤ 7 g/dl, and PCC or FFP will be transfused at the same dose described above if the APTT is prolonged (>1.5-times normal) based on the allocation of the patients. Other blood product transfusions will be performed at the discretion of critical care physicians and surgeons based on patient conditions and laboratory test results.

Researchers who deliver the PCC or FFP to participants during and after surgery will receive specific training to guarantee that the interventions are provided according to the randomized groups. The anaesthesia records, medical records and medical orders will be reviewed to confirm the interventions.

Follow-up and withdrawal

The study follow-up is scheduled as follows: 24 hours, 48 hours, 72 hours and 7 days after surgery to record observations relevant to the study and the results of laboratory testing. The laboratory tests will include the haemoglobin concentration, hematocrit level, platelet count, INR, PT, APTT, fibrinogen level, and blood biochemistry parameters such as creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) concentrations. Blood loss will be recorded during the surgical procedure and within 24 hours after surgery. Other examinations will include electrocardiography, X-ray, and echocardiography. EpiData Software will be used for data entry and storage. Double data entry will be used to ensure data quality.

Every reasonable effort will be made to maintain protocol compliance and retain patient participation in the study. Participation will be terminated if the patient withdraws from the study. A study withdrawal form will be completed for these patients, and the reason for withdrawal will be captured. All subjects withdrawn from the study will be managed in accordance with the hospital's standard procedures.

Outcomes

Primary outcome

The primary outcome is the volume of blood loss during and within 24 hours after surgery.

Secondary outcomes

The secondary outcomes include (1) the total units of allogeneic RBCs transfused during and within 7 days after surgery; and (2) re-exploration due to postoperative bleeding within 7 days after surgery.

Intraoperative blood loss will be assessed by measuring the amount collected by aspiration and weighing the surgical gauze compresses. Blood loss from the floor, surgical gowns and surgical drapes are not included. Postoperative blood loss will be recorded as the blood volume collected through the suction drains at 24 hours.

Statistical analysis

Sample size

This is a clinical non-inferiority trial based on the hypothesis that PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB. According to clinical experience, the standard deviation of blood loss during and within 24 hours after cardiac surgery under CPB is 800 ml. For a difference of 200 ml to be considered clinically significant, a total sample size of 504 patients is needed to achieve 80% power at the 2.5% significance level. Considering a 10% dropout rate, a total of 560 patients (280 per group) is necessary.

Statistical methods

Modified intent-to-treat analysis will be used for all valid variables. All randomized subjects in the study, regardless of adherence to the study process or whether an adverse event occurs before or after the intervention, should be included in the analysis. Sensitivity analysis will be performed to assess the bias that may be introduced due to nonadherence to the protocol or missing data. Baseline characteristics will be tabulated and compared between the PCC and FFP groups using standardized differences, and a value larger than 0.2 will be regarded as a clinically relevant difference between groups.

The primary outcome, the volume of blood loss during and within 24 hours after surgery, will be compared using the t-test with log transformation of the variable. Continuous secondary outcomes and the total units of allogeneic RBCs transfused during and within 7 days after surgery will be compared using a t-test with log transformation of the variable. The rate of re-exploration due to bleeding within 7 days after surgery will be compared using the chi-square test. Treatment effect will be measured by odds ratio and mean difference for binary and continuous outcomes with corresponding 95% confidence intervals. No correction for multiple comparisons will be conducted in the analysis of the secondary outcomes; hence, the findings for secondary outcomes will be interpreted only as explanatory results. A two-sided P-value < 0.05 was considered indicative of statistical significance.

Adverse events

Adverse events are defined as any undesirable event occurring in a patient during the study regardless of whether the event is considered to be related to PCC or FFP, such as perioperative myocardial infarction, renal dysfunction, hepatic dysfunction and neurological complications. All adverse events reported spontaneously by the patient or observed by the investigator or staff will be recorded and should be judged for relevance to the study intervention by researchers. A detailed description should be made and recorded in the summary report, including the date, manifestations, laboratory results, classification (Table 2) and prognosis (Table 3).

A severe adverse event (SAE) is any untoward medical occurrence or effect that results in death, is life-threatening (at the time of the event), requires hospitalization or prolongation of existing inpatient hospitalization, or results in persistent or significant disability or incapacity, or any other important medical event that does not result in any of the outcomes listed above due to medical or surgical intervention but could be based upon appropriate judgement by the investigator. Any SAE should be recorded on the case report form (CRF). SAEs that occur from the beginning of the study to 24 hours after surgery should be reported to the Ethics Committee within 24 hours, even if it may not be associated with the study regimen. The related follow-up data should be reported to the sponsor after 24 hours.

Protocol amendments

The current protocol is version 2.0, date 2020-3-8. Any changes in the protocol during the trial that may affect the conduct of the trial, the safety and the benefit to patients will require a formal amendment to the protocol.

Patient and public involvement

This research will be done without patient involvement. Patients will not be invited to comment on the study design or contribute to the acquisition, analysis, or interpretation of data for the work. Patients will not be consulted to develop relevant outcomes. Patients will not be invited to draft the manuscript for integrity or accuracy.

DISCUSSION

Coagulopathy is an important risk factor for bleeding and transfusion and is associated with both early and late morbidity in patients undergoing cardiac surgery; however, previous treatments for coagulopathy, antifibrinolytic drugs and blood component transfusion are ineffective and associated with adverse outcomes. PCC was originally developed for the treatment of patients with haemophilia B; however, due to the recent availability of plasma-derived high purity factor IX concentrates and more recently, of a recombinant factor IX product, their indications have progressively shifted from this bleeding disorder towards replacement therapy for congenital or acquired deficiency of vitamin K-dependent clotting factors[33].

PCC has several advantages over FFP. Various comparative studies have demonstrated that PCC is more effective than FFP for correcting the INR[34,35]. The concentration of vitamin K-dependent coagulation factors is 25 times higher in PCC than in plasma[25], which leads to a more significant and faster effect of reducing INR. Another major advantage of PCC over FFP is that smaller volumes of the former are required to correct coagulopathy[36]. Thus, while FFP is often administered at doses of approximately 15 ml/kg, the recommended doses of PCC required to achieve 50-100% of the levels of prothrombin complex factors can be delivered in injection volumes of 1-2 ml/kg. The reduced volume with PCC minimizes the risk of fluid overload, especially in patients with a compromised cardiovascular system, and decreases the time needed for infusion. PCC also require less preparation time than FFP, as they can usually be stored at room

temperature, allowing administration without warming, whereas FFP must first be thawed and then warmed[37,38]. In addition, PCC has a better safety profile than FFP because they undergo viral inactivation steps to minimize the risk of transmission of a variety of infective agents, including prions[37]. Another important consideration is the association of FFP with the risk of TRALI, a major cause of death after transfusion[39]. This risk is not present with the use of PCC as the antibodies responsible for TRALI are removed during the manufacturing processes[37].

Adverse events associated with PCC include immediate allergic reactions, heparin-induced thrombocytopenia (HIT, for preparations containing heparin) and thromboembolic complications. The primary safety concern with PCCs has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation and deep vein thrombosis[40]. In a review by Leissinger and colleagues[38], the PCC used to reverse warfarin anticoagulation was associated with a low risk of thrombotic adverse events (7/506 cases, 1.4%). Although these events were associated with PCC administration, they could be attributed to the patients' underlying thrombotic risk factors in most cases. In addition, the already low incidence of such adverse events has further decreased over the last few years due to improvements in the composition of the more recent commercially available PCC (i.e., inclusion of coagulation inhibitors, reduced use of activated coagulation factors, and improved balance of coagulation factors). A meta-analysis involving a total of 165 clinical studies from 1999 to 2008 showed that the incidence of PCC-associated thrombosis was only 0.9%[25].

PCC is recommended for acute reversal of oral anticoagulation[41,42]. Some centres also administer PCC in cases of massive bleeding and prolonged clotting times[43], although for perioperative bleeding, the data are very limited. Further prospective, randomized controlled trials assessing the efficacy and safety of perioperative application of PCC during cardiac surgery are needed.

DECLARATIONS

Ethics approval and consent to participate

This study has been approved by the ethics committee of Peking Union Medical College Hospital (ZS-2242). Written informed consent will be obtained from all subjects involved.

Consent for Publication

Consent for publication will be obtained.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Access to data

The sponsor of this study, also the corresponding author, and the authorized data analyst will have access to the final trial dataset.

Confidentiality

Only the ID and clinical data of participants will be recorded on the CRF, and no specific personal information will be retained. ID numbers will be encoded to protect confidentiality.

Competing interests

The authors declare that they have no competing interests.

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Trials status

This protocol is version 2.0, date 2020-3-8. The recruitment is planned to begin on March 1st, 2021, and end on March 1st, 2023, lasting 2 years.

Author Contributions

Lijian Pei, Chen Sun and Jia Shi participated in the design and coordination of the study. Chen Sun, Lijian Pei, Hong Lv, Yuelun Zhang and Jia Shi collected references and

developed the protocol. Chen Sun, Jia Shi and Yuelun Zhang performed the statistical analysis. Lijian Pei, Chen Sun and Jia Shi drafted the manuscript. All authors read and approved the final manuscript.

Lijian Pei and Chen Sun contribute equally to the manuscript.

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Table 1 Recommended PCC dose

INR value	2.0-4.0	4.0-6.0	>6
Dose of PCC to infuse	25 IU/kg	35 IU/kg	50 IU/kg

Table 2 Classification of adverse events

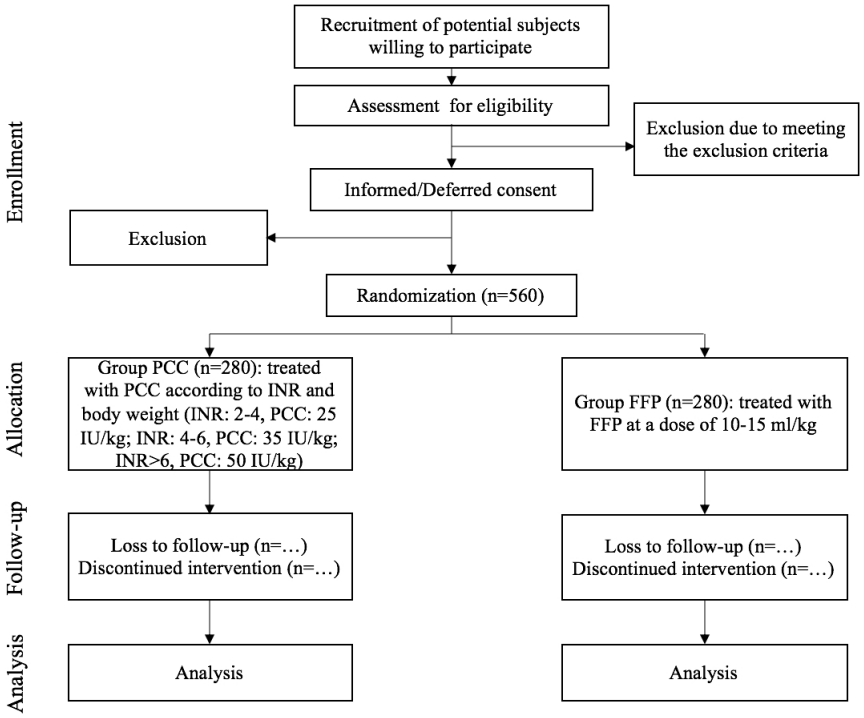
Classification	Definition
Mild	With manifestations but no limitation of physical activity
Moderate	With limitation of physical activity
Severe	Unable to carry on any physical activity

Table 3 Prognosis of adverse events

Prognosis	Definition
D	Death
P	Permanent or organic labor loss
H	Hospitalization
N	None of the above

Figure 1 Study design and participant flow chart

Figure 2 Study period



Study design and participant flow chart

	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				Close-out
TIMEPOINT	***Within 7d before surgery***	***1d before surgery***	***1h before surgery***	***Intra-operation***	***24h after surgery***	***48h after surgery***	***72h after surgery***	***7d after surgery***
ENROLMENT:								
Eligibility screen		X						
Informed consent		X						
ALLOCATION:			X					
INTERVENTIONS:								
PCC				X				
FFP				X				
ASSESSMENTS:								
Baseline variables:								
Hb	X			X	X	X	X	
Hct	X			X	X	X	X	
Plt	X			X	X	X	X	
INR	X			X	X	X	X	
PT	X			X	X	X	X	
APTT	X			X	X	X	X	
Fibrinogen	X			X	X	X	X	
Blood biochemistry	X			X	X	X	X	
Outcome variables:								
Blood loss				X	X			
RBC transfusion				X	X	X	X	X
Re-exploration					X	X	X	X

Study period

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Trial registration, Page 2)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Yes.)**
Protocol version	3	Date and version identifier **(Page 1)**
Funding	4	Sources and types of financial, material, and other support **(Funding, Page 14)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Affiliation, Author's Contributions, Page 13, 14)**
	5b	Name and contact information for the trial sponsor **(Corresponding author, Page 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 **(N/A. No sponsor and funders in this study.)**
	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) **(N/A. No coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups in this study.)**
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 **(Background, Page 3)**

	6b	Explanation for choice of comparators **(Randomization and blinding, Page 5)**
Objectives	7	Specific objectives or hypotheses **(Objective, Page 4)**
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) **(Design, Page 4)**

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 **(Design, Page 4)**
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) **(Inclusion criteria, Exclusion criteria, Page 4-5)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Interventions, Page 5-7)**
	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) **(Follow-up and withdrawal, Page 7)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Interventions, Page 5-7).**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A. There is no special relevant concomitant care and interventions that are permitted or prohibited during the trial.)**
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 **(Outcomes, Page 8)**
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) **(Figure 1, in Attach Files)**
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 **(Sample size, Page 8)**

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Design, Inclusion criteria, Exclusion criteria, Page 4-5)**
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 **(Randomization and blinding, Page 5)**
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 **(Randomization and blinding, Page 5)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Randomization and blinding, Page 5)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Randomization and blinding, Page 5)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Randomization and blinding, Page 5)**
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 **(Follow-up and withdrawal, Page 7-8)**
	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 **(Follow-up and withdrawal, Page 7-8)**
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 **(Follow-up and withdrawal, Page 7-8)**
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 **(Statistical methods, Page 8-9)**

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A.There isn't any additional analyses.)**
	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) **(Statistical methods, Page 8-9)**
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 **(N/A. This study focuses on the perioperative period which lasts for no more than 7 days after surgery, and there won't be too many data collected in the study, so it is not necessary to develop a DMC.)**
	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 **(N/A. Interim analyse is not applicable to this study.)**
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 **(Adverse events, Page 9)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(N/A. There is no auditing trial conduct.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Ethics approval and consent to participate, Page 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) **(Protocol amendments, Page 10)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Ethics approval and consent to participate, Page 14)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A. No additional consent provisions in this study.)**
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 **(Confidentiality, Page 14)**

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Consent for Publication, Funding, Page 14)**
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 **(Access to data, Page 14)**
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 **(N/A. No provision 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 **(N/A. No plan for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups.)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A. There is no authorship eligibility guidelines and any intended use of professional writers.)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(N/A. No plan 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 **(Informed consent, Appendices)**
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 **(N/A. No biological specimens were collected as part of this trial.)**

*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.

BMJ Open

Efficacy of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) in reducing perioperative blood loss in cardiac surgery: study protocol for a non-inferiority, randomized controlled trial

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Keywords:	Cardiac surgery < SURGERY, Anaesthesia in cardiology < ANAESTHETICS, Clinical trials < THERAPEUTICS

Efficacy of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) in reducing perioperative blood loss in cardiac surgery: study protocol for a non-inferiority, randomized controlled trial

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ABSTRACT

Objective: To explore whether prothrombin complex concentrate (PCC) is not inferior to fresh frozen plasma (FFP) with regard to reducing perioperative blood loss in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB).

Setting: National Centre for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital in China.

Participants: Patients undergoing elective CABG, valve replacement or valvuloplasty under CPB, between 18 and 80 years old, will be included.

Design: This study is a non-inferiority, randomized controlled clinical trial. A total of 594 subjects will be randomly assigned to 2 groups (group PCC and group FFP) when INR > 1.7, prolonged PT or APTT (> 1.5 times baseline) is measured 20 minutes after CPB (ACT within 130 s), or excessive bleeding is observed. 4-factor PCC (15 IU/kg) and FFP (10 mL/kg) will be given to group PCC and

group FFP respectively. Preoperative management, anaesthetic and surgical techniques will be standardized for both groups.

Primary and Secondary Outcome Measures: The primary outcome is the volume of blood loss during and within 24 hours after surgery. The secondary outcomes include (1) the total units of allogeneic red blood cells (RBCs) transfused during and within 7 days after surgery and (2) re-exploration due to postoperative bleeding within 7 days after surgery.

Trial registration: Registered under NCT04244981 at ClinicalTrials.gov on 28 January 2020, https://clinicaltrials.gov/ct2/show/NCT04244981?cond=NCT04244981&draw=2&rank=1.

Ethics and dissemination: This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (ZS-2242).

Key words: prothrombin complex concentrate, fresh frozen plasma, perioperative blood loss, cardiac surgery, cardiopulmonary bypass

Strengths and Limitations:

- This study focuses on the efficacy of prothrombin complex concentrate (PCC), compared with fresh frozen plasma (FFP), in reducing perioperative blood loss under cardiopulmonary bypass in cardiac surgery.
- Considering the insufficiency and disadvantages of FFP, the study may provide an alternative strategy for the treatment of major blood loss in cardiac surgery.
- One of the limitations of this study is that the doses and time of intervention are based on guidelines and clinical practice, not having previous evidence in our own research team to provide stronger support.
- Another limitation is the safety of PCC, compare with FFP, for reducing perioperative blood loss in cardiac surgery is not evaluated in present study.

INTRODUCTION

Major bleeding and allogeneic blood transfusion are major complications of cardiac surgery[1,2], with increased risk of serious postoperative morbidities including infections, atrial fibrillation, respiratory complications, acute kidney injury, short-term and long-term mortality, and increased medical costs[3-5]. Compared to all other surgeries, cardiac surgery is among the highest overall rate of RBC transfusion, accounting for 10%-15% of all RBC transfusions in the United States and the United Kingdom[6,7]. Approximately 10% of all cardiac surgery patients suffer from severe or massive blood loss, and up to 5% require emergent re-exploration in an attempt to correct ongoing bleeding and establish adequate hemostasis[8,9].

Coagulopathy is one of the main reasons for massive perioperative bleeding and allogeneic blood transfusion in cardiac surgery and cardiopulmonary bypass (CPB)[10]. In addition to decreasing platelet and fibrinogen levels, coagulation factor deficiency also plays an important role in post-CPB coagulopathy[11]. Fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) are currently used primarily to treat perioperative coagulopathy in cardiac surgery[12] and suitable for increasing the concentration of vitamin K-dependent coagulation factors. Compared with FFP, PCC offers several advantages in the management of cardiac surgery coagulopathy, such as faster infusion rates, lower volume overload, shorter preparation time, no blood-type matching needed and lower rate of transfusion reaction[13]. In addition, FFP is always insufficient in clinical therapy. Therefore, we hope to gradually reduce the use of FFP and switch to use PCC to treat perioperative coagulopathy in cardiac surgery.

A body of evidence have suggested that PCCs can provide more rapid and effective treatment for warfarin and vitamin K antagonists (VKA) reversal compared with FFP, with rapid international normalized ratio (INR) correction and greater increase in clotting factors[14-16]. However, there are only a few studies, mostly retrospective studies, concentrating on PCC for the treatment of post-CPB bleeding, which indicate that the use of PCC is associated with less chest tube output and red blood cell transfusion

versus FFP[17-20]. Properly designed randomized controlled clinical trials (RCT) should be done to evaluate the efficacy and safety of PCC compared with FFP.

Considering the gap, we want to design an RCT to identify the efficacy of PCC compared with FFP in the treatment for coagulopathy in cardiac surgery, exploring whether PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB.

METHODS

Study design

This is a non-inferiority, randomized controlled clinical trial. The trial will be conducted at the National Center for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital, China. A total of 594 participants will be randomized. The trial schema is shown in Figure 1, and the study period is shown in Figure 2. The study will be monitored by an independent Trial Steering Committee and Data Safety Monitoring Committee.

Study population

Inclusion criteria

Eligible patients must meet all of the following criteria:

1. Age between 18 and 80 years.
2. Undergoing elective coronary artery bypass grafting (CABG) or valve replacement or valvuloplasty through CPB.
3. Developing coagulation factor deficiency or coagulopathic bleeding during the surgery, meeting the indications of PCC or FFP treatment.
4. Signing of the informed consent form.

Exclusion criteria

The exclusion criteria are as follows:

1. History of cardiac surgery.
2. Hepatic dysfunction before surgery.

3. Coagulopathy before surgery.
4. Withdrawal of clopidogrel or aspirin less than 7 days and low molecular weight heparin less than 24 hours before surgery.
5. Allergy to allogeneic blood products.
6. Pregnancy.
7. Other serious diseases that may affect patient survival time, such as cancers.

Randomization and blinding

Stratified randomization will be used to assign the patients to two groups. The informed consents of those patients meeting the admission criteria will be obtained before surgery. Then patients will be randomly assigned to 2 groups by a specific computer randomization system, when INR > 1.7, prolonged PT or APTT (> 1.5 times baseline) is measured 20 minutes after CPB, or excessive bleeding is observed. Nurse anaesthetists will prepare the corresponding products for each patient according to the group assignments in an anaesthesia preparation room. PCC or FFP will be pumped into 50 ml syringes firstly, covered with opaque paper to hide the contents. The enrolment number of each patient will be marked on the syringes. Finally, the corresponding interventional products will be given to patients from syringes, followed by the light-protected infusion set. Participants, anaesthesiologists, surgeons, and outcome assessors will all be blinded to the group assignments throughout the trial. In the case of the need for emergency rescue, if it is necessary to know the intervention for a participant, blinding will be broken. The allocation will be disclosed to healthcare providers in case of emergency in compliance with ethics considerations.

Interventions

Participants will be randomly assigned to 2 groups named the prothrombin complex concentrate group (group PCC) and the fresh frozen plasma group (control group or group FFP) respectively, with 297 cases in each group.

Preoperative management, anaesthetic and surgical techniques will be standardized for all patients. Various demographic as well as preoperative physiological and laboratory

parameters will be recorded for each patient. During the operation, all patients will be under general anaesthesia. The surgical procedures will be performed through a median sternotomy approach, and CPB will be undertaken in a standardized fashion. A mild hypothermia condition (32-34℃) will be achieved, and heparin (400 IU/kg) will be intravenously administered before initiation of CPB, with activated clotting time (ACT) maintained above 480 seconds during CPB. In addition, tranexamic acid will be intravenously administered after the induction of anaesthesia until the end of the operation (20 mg/kg for the first hour and 2 mg/kg thereafter). After CPB, circulating heparin will be antagonized with protamine sulfate at a ratio of 1 mg of protamine per 100 IU of heparin, making ACT within 130 s. Prolonged ACT will be treated with an additional dose of protamine sulfate. The cell saver machine will be used during surgery, and the following parameters should be checked and corrected off bypass as necessary: (1) patient's core temperature, (2) arterial blood gases (ABGs), (3) post CPB coagulation screening results: a) the platelet count, b) the international normalized ratio (INR), c) the activated partial thromboplastin time (APTT) and prothrombin time (PT) and d) serum fibrinogen levels. Off bypass, all patients' core temperatures will be raised above 37℃.

PCC or FFP will be transfused when coagulation factor deficiency or coagulopathic bleeding is observed. In this study, the indications of PCC or FFP treatment include INR > 1.7, prolonged PT or APTT (> 1.5 times baseline) measured 20 minutes off-pump (ACT within 130 s), or excessive bleeding observed during the surgery[21-23]. In the presence of these conditions, 4-factor PCC (15 IU/kg) or FFP (10 mL/kg) will be given according to the group assignments, guided by manufacturer's instructions and previous research[21]. The decision to administer FFP or PCC will be at the discretion of the clinical team in the operating room. Half an hour after transfusion, the re-evaluation will be done and an additional dose will be administered if required. Other allogeneic blood products will be needed if cell saver is insufficient for patients, and transfusion will be guided by the haemoglobin concentration, the platelet count, the INR, the PT,

the APTT and serum fibrinogen levels. Homologous red blood cells (RBCs) will be intraoperatively administered to maintain a haemoglobin concentration > 7 g/dl or a haematocrit higher than 20%. Platelets will be transfused when their count is $\leq 60\times10^9$/l. Serum fibrinogen levels less than 1.5 g/l will be corrected with fibrinogen concentrate at doses of 25-50 mg/kg[31]. Additional blood product transfusions also will be performed at the discretion of the clinical team in the operating room.

After surgery, patients will be sent to the intensive care unit (ICU) and then back to the ward after their conditions stable. Patients' haemoglobin concentrations, haematocrit levels, platelet counts, INRs, PTs, APTTs, fibrinogen levels and blood biochemistry parameters will be monitored daily in the ICU. RBCs will be transfused if the haemoglobin concentration is ≤ 7 g/dl. Other blood product transfusions will be performed at the discretion of critical care physicians and surgeons based on patient conditions and laboratory test results.

Researchers who deliver the PCC or FFP to participants during the surgery will receive specific training to guarantee that the interventions are provided according to the randomized groups. The anaesthesia records, medical records and medical orders will be reviewed to confirm the interventions.

Follow-up and withdrawal

The study follow-up is scheduled as follows: 24 hours, 48 hours, 72 hours and 7 days after surgery to record observations relevant to the study and the results of laboratory testing. The laboratory tests will include the haemoglobin concentration, hematocrit level, platelet count, INR, PT, APTT, fibrinogen level, and blood biochemistry parameters such as creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) concentrations. Blood loss will be recorded during the surgical procedure and within 24 hours after surgery. Other examinations will include electrocardiography, X-ray, and echocardiography. EpiData Software will be used for data entry and storage. Double data entry will be used to ensure data quality.

Every reasonable effort will be made to maintain protocol compliance and retain patient participation in the study. Participation will be terminated if the patient withdraws from the study. A study withdrawal form will be completed for these patients, and the reason for withdrawal will be captured. All subjects withdrawn from the study will be managed in accordance with the hospital's standard procedures.

Outcomes

Primary outcome

The primary outcome is the volume of blood loss during and within 24 hours after surgery.

Secondary outcomes

The secondary outcomes include (1) the total units of allogeneic RBCs transfused during and within 7 days after surgery, and (2) re-exploration due to postoperative bleeding within 7 days after surgery.

Intraoperative blood loss will be assessed by measuring the amount collected by aspiration and weighing the surgical gauze compresses. Blood loss from the floor, surgical gowns and surgical drapes are not included. Postoperative blood loss will be recorded as the blood volume collected through the suction drains at 24 hours.

Statistical analysis

Sample size

This is a clinical non-inferiority trial based on the hypothesis that PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB. According to previous studies in our research team, the mean volume of blood loss during and within 24 hours after cardiac surgery under CPB is 726.3 ml, and the standard deviation is 824.38 ml. A non-inferiority margin is set at 200 ml based on clinical practice. To achieve 80% power at the 2.5% significance level, a sample size of 267 patients for each group is needed. Considering a 10% dropout rate, a total of 594 patients (297 per group) is necessary.

Statistical methods

Modified intent-to-treat analysis will be used for all valid variables. All randomized subjects in the study, regardless of adherence to the study process or whether an adverse event occurs before or after the intervention, should be included in the analysis. Sensitivity analysis will be performed to assess the bias that may be introduced due to nonadherence to the protocol or missing data. Baseline characteristics will be tabulated and compared between the PCC and FFP groups using standardized differences, and a value larger than 0.2 will be regarded as a clinically relevant difference between groups. The primary outcome, the volume of blood loss during and within 24 hours after surgery, will be compared using the t-test with log transformation of the variable. Continuous secondary outcomes and the total units of allogeneic RBCs transfused during and within 7 days after surgery will be compared using a t-test with log transformation of the variable. The rate of re-exploration due to bleeding within 7 days after surgery will be compared using the chi-square test. Treatment effect will be measured by odds ratio and mean difference for binary and continuous outcomes with corresponding 95% confidence intervals. No correction for multiple comparisons will be conducted in the analysis of the secondary outcomes; hence, the findings for secondary outcomes will be interpreted only as explanatory results. A two-sided P-value < 0.05 was considered indicative of statistical significance.

Adverse events

Adverse events are defined as any undesirable event occurring in a patient during the study regardless of whether the event is considered to be related to PCC or FFP, such as perioperative myocardial infarction, renal dysfunction, hepatic dysfunction and neurological complications. All adverse events reported spontaneously by the patient or observed by the investigator or staff will be recorded and should be judged for relevance to the study intervention by researchers. A detailed description should be made and recorded in the summary report, including the date, manifestations, laboratory results, classification (Table 1) and prognosis (Table 2).

A severe adverse event (SAE) is any untoward medical occurrence or effect that results in death, is life-threatening (at the time of the event), requires hospitalization or prolongation of existing inpatient hospitalization, or results in persistent or significant disability or incapacity, or any other important medical event that does not result in any of the outcomes listed above due to medical or surgical intervention but could be based upon appropriate judgement by the investigator. Any SAE should be recorded on the case report form (CRF). SAEs that occur from the beginning of the study to 24 hours after surgery should be reported to the Ethics Committee within 24 hours, even if it may not be associated with the study regimen. The related follow-up data should be reported to the sponsor after 24 hours.

Protocol amendments

The current protocol is version 3.0, date 2021-9-21. Any changes in the protocol during the trial that may affect the conduct of the trial, the safety and the benefit to patients will require a formal amendment to the protocol.

Patient and public involvement

This research will be done without patient involvement. Patients will not be invited to comment on the study design or contribute to the acquisition, analysis, or interpretation of data for the work. Patients will not be consulted to develop relevant outcomes. Patients will not be invited to draft the manuscript for integrity or accuracy.

DISCUSSION

Coagulopathy is an important risk factor for bleeding and blood transfusion in patients undergoing cardiac surgery, associated with both early and late morbidity. Administration of FFP and PCC is current treatment regimens for clotting factor deficiency, which might be one of the major reasons of coagulopathy after CPB during cardiac surgery[13]. Considering the advantages of PCC over FFP[24-26] and the insufficiency of FFP in clinical practice setting, more and more research has been conducted to explore the efficacy and safety of PCC versus FFP in various conditions[27,28]. Till now, the use of PCC is recommended highly for severe bleeding

from warfarin, as well as for patients undergoing urgent surgery or invasive procedures based on guidelines from several organizations[22,23,29].

However, for perioperative bleeding and prolonged clotting times during cardiac surgery, the data are very limited. Several retrospective studies showed less perioperative bleeding and blood transfusion in patients with PCC, compared with FFP. In an observational study by Cappabianca et al[17], when 3-factor PCC was administered prior to chest closure or in the first few postoperative hours as a first-line treatment for post-CPB bleeding, there were less chest tube output and red cell transfusion versus FFP. In a retrospective cohort study, Arnekian et al[30] showed that low-dose PCC (10 U/kg) was associated with reduced blood loss during the initial hours after cardiac surgery. Patients who received combined FFP and PCC underwent more re-explorations than other groups. Clinical validation studies, such as properly designed RCTs still are needed to provide stronger evidence. So this time, we designed this non-inferiority, randomized controlled clinical trial to explore the efficacy of PCC, compare with FFP, for the treatment of perioperative blood loss during general cardiac surgery.

In our study, we will choose the patients undergoing elective CABG, valve replacement or valvuloplasty through CPB in National Centre for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital, China. Both hospitals are top medical institutions in China, with a large number of patients and standardized clinical diagnosis and treatment strategies, ensuring the feasibility and reliability of this study.

After obtaining the informed consents, patients meeting the administration criteria will be pre-enrolled and then actually enrolled and randomized into different groups (group PCC or group FFP) when meeting the indications of PCC or FFP treatment. According to guidelines and previous research, such indications include INR > 1.7, prolonged PT or APTT (> 1.5 times baseline), or excessive bleeding observed during the surgery[21-23]. In other words, any symptoms reflecting the coagulation factor deficiency or coagulopathic bleeding during the surgery will trigger the transfusion of PCC or FFP.

The recommended dose of PCC in guidelines is mainly used to reverse the effects of VKA and correct INR[15,23,30], which is not quite suitable for our study. Patients included in our study will undergo non-complex cardiac surgery and will not be on anticoagulation therapy prior to surgery, so they rarely develop INR > 2 and require such high level of PCC[31]. To choose the proper dose of PCC, we firstly selected 10 mL/kg for FFP according to the guidelines[22,23], previous research[21] and clinical practice. Then taking the dose balance of two intervention products, previous research which included similar patients as our study[21], and the manufacturer's instructions of PCC used in this study into consideration, we finally chose 15 IU/kg for PCC.

The primary safety concern with PCCs has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation and deep vein thrombosis[32]. A meta-analysis of 27 clinical studies involving 1,032 patients presenting with bleeding or undergoing surgery showed that emergency reversal of warfarin with PCC was associated with a 1.4% incidence of thromboembolic events. The incidence was 1.8% with 4-factor PCC (20 studies) and 0.7% with 3-factor PCC (7 studies), with a mortality rate of 10.6%[33]. Although these events were associated with PCC administration, they could be attributed to the patients' underlying thrombotic risk factors in most cases. In addition, the already low incidence of such adverse events has further decreased over the last few years due to improvements in the composition of the more recent commercially available PCC (i.e., inclusion of coagulation inhibitors, reduced use of activated coagulation factors, and improved balance of coagulation factors). Current evidence suggests that thromboembolic events and mortality are not increased with the use of PCCs[13].

Our study also has several limitations. First, this is an exploratory study without pilot study before. The doses and time of intervention are based on guidelines and clinical practice, not having previous evidence in our own research team to provide stronger support. Further clinical validation studies for doses and time of PCC administration

are needed to establish the most effective and safe way of administering PCC to cardiac surgical patients. On the other hand, our study only pay attention to the efficacy of PCC versus FFP. We hope to evaluate the safety of PCC, compare with FFP, for reducing perioperative blood loss in cardiac surgery in the future.

In conclusion, this study aims to identify the efficacy of PCC compared with FFP, exploring whether PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB. Considering the gap of current research, our study will provide stronger clinical evidence and data support for PCC treatment in perioperative coagulopathy bleeding during general cardiac surgery, and also provide reference and guidance for clinicians in perioperative blood management during cardiopulmonary bypass.

DECLARATIONS

Consent for publication

Consent for publication will be obtained.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Access to data

The sponsor of this study, also the corresponding author, and the authorized data analyst will have access to the final trial dataset.

Confidentiality

Only the ID and clinical data of participants will be recorded on the CRF, and no specific personal information will be retained. ID numbers will be encoded to protect confidentiality.

Competing interests

The authors declare that they have no competing interests.

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Trials status

This protocol is version 3.0, date 2021-9-21. The recruitment is planned to begin on January 1st, 2022, and end on December 31st, 2024, lasting 3 years.

Author contributions

Lijian Pei, Chen Sun and Jia Shi participated in the design and coordination of the study. Chen Sun, Lijian Pei, Hong Lv, Yuelun Zhang and Jia Shi collected references and developed the protocol. Chen Sun, Jia Shi and Yuelun Zhang performed the statistical

analysis. Lijian Pei, Chen Sun and Jia Shi drafted the manuscript. All authors read and approved the final manuscript.

Lijian Pei and Chen Sun contributed equally to the work.

Acknowledgements

Not applicable.

Ethics and dissemination

This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (ZS-2242). Written informed consent will be obtained from all subjects involved.

Exclusive license statement

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Table 1 Classification of adverse events

Classification	Definition
Mild	With manifestations but no limitation of physical activity
Moderate	With limitation of physical activity
Severe	Unable to carry on any physical activity

Table 2 Prognosis of adverse events

Prognosis	Definition
D	Death
P	Permanent or organic labor loss
H	Hospitalization
N	None of the above

Figure 1 Study design and participant flow chart

Figure 2 Study period

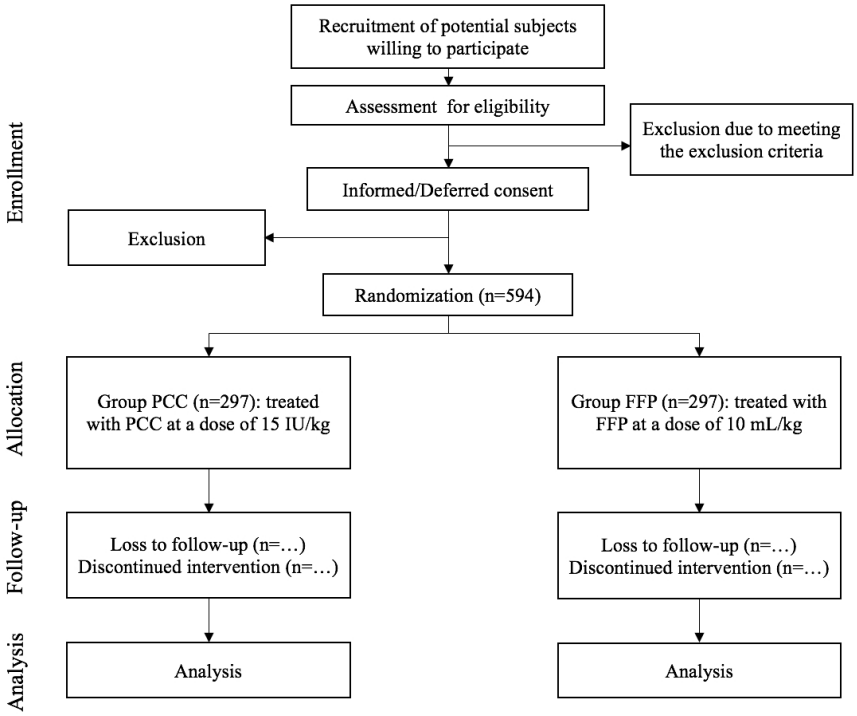

Figure 1: Study design and participant flow chart

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	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				Close-out
TIMEPOINT	***Within 7d before surgery***	***1d before surgery***	***1h before surgery***	***Intra-operation***	***24h after surgery***	***48h after surgery***	***72h after surgery***	***7d after surgery***
ENROLMENT:								
Eligibility screen		X						
Informed consent		X						
ALLOCATION:			X					
INTERVENTIONS:								
PCC				X				
FFP				X				
ASSESSMENTS:								
Baseline variables:								
Hb	X			X	X	X	X	
Hct	X			X	X	X	X	
Plt	X			X	X	X	X	
INR	X			X	X	X	X	
PT	X			X	X	X	X	
APTT	X			X	X	X	X	
Fibrinogen	X			X	X	X	X	
Blood biochemistry	X			X	X	X	X	
Outcome variables:								
Blood loss				X	X			
RBC transfusion				X	X	X	X	X
Re-exploration					X	X	X	X

Figure 2: Study period

561x519mm (57 x 57 DPI)

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Trial registration, Page 2)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Yes.)**
Protocol version	3	Date and version identifier **(Page 1)**
Funding	4	Sources and types of financial, material, and other support **(Funding, Page 14)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Affiliation, Author's Contributions, Page 1, 14)**
	5b	Name and contact information for the trial sponsor **(Corresponding author, Page 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 **(N/A. No sponsor and funders in this study.)**
	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) **(Study design, Page 4)**
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 **(Introduction, Page 3)**
	6b	Explanation for choice of comparators **(Randomization and blinding, Page 5)**
Objectives	7	Specific objectives or hypotheses **(Page 4)**

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) **(Study design, Page 4)**
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 **(Study design, Page 4)**
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) **(Inclusion criteria, Exclusion criteria, Page 4-5)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Interventions, Page 5-7)**
	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) **(Follow-up and withdrawal, Page 7-8)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Interventions, Page 5-7).**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A. There is no special relevant concomitant care and interventions that are permitted or prohibited during the trial.)**
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 **(Outcomes, Page 8)**
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) **(Figure 1, in Attach Files)**
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 **(Sample size, Page 8)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Study design, Inclusion criteria, Exclusion criteria, Page 4-5)**
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 **(Randomization and blinding, Page 5)**
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 **(Randomization and blinding, Page 5)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Randomization and blinding, Page 5)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Randomization and blinding, Page 5)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Randomization and blinding, Page 5)**
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 **(Follow-up and withdrawal, Page 7-8)**
	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 **(Follow-up and withdrawal, Page 7-8)**
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 **(Follow-up and withdrawal, Page 7-8)**
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 **(Statistical methods, Page 9)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A.There isn't any additional analyses.)**

	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) **(Statistical methods, Page 9)**
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 **(N/A. This study focuses on the perioperative period which lasts for no more than 7 days after surgery, and there won't be too many data collected in the study, so it is not necessary to develop a DMC.)**
	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 **(N/A. Interim analyse is not applicable to this study.)**
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 **(Adverse events, Page 9-10)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(N/A. There is no auditing trial conduct.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Ethics and dissemination, Page 15)**
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) **(Protocol amendments, Page 10)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Ethics and dissemination, Page 15)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A. No additional consent provisions in this study.)**
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 **(Confidentiality, Page 14)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Consent for publication, Funding, Page 14)**

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 **(Access to data, Page 14)**
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 **(N/A. No provision 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 **(N/A. No plan for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups.)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A. There is no authorship eligibility guidelines and any intended use of professional writers.)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(N/A. No plan 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 **(Informed consent, Appendices)**
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 **(N/A. No biological specimens were collected as part of this trial.)**

*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.

BMJ Open

Efficacy of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) in reducing perioperative blood loss in cardiac surgery: study protocol for a non-inferiority, randomized controlled trial

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Primary Subject Heading:	Anaesthesia
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Keywords:	Cardiac surgery < SURGERY, Anaesthesia in cardiology < ANAESTHETICS, Clinical trials < THERAPEUTICS

Efficacy of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) in reducing perioperative blood loss in cardiac surgery: study protocol for a non-inferiority, randomised controlled trial

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Version 3.0, Date 2021-9-21

ABSTRACT

Objective: To explore whether prothrombin complex concentrate (PCC) is not inferior to fresh frozen plasma (FFP) with regard to reducing perioperative blood loss in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB).

Setting: National Centre for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital in China.

Participants: Patients undergoing elective CABG, valve replacement or valvuloplasty under CPB, between 18 and 80 years old, will be included.

Design: This study is a non-inferiority, randomised controlled clinical trial. A total of 594 subjects will be randomly assigned to 2 groups (group PCC and group FFP) and given corresponding interventions when at least one of the following criteria is met: a) INR > 1.7 measured 20 minutes after CPB, b) prolonged PT or APTT (> 1.5 times baseline) measured 20 minutes after CPB, and c)

excessive bleeding observed. 4-factor PCC (15 IU/kg) and FFP (10 mL/kg) will be given to group PCC and group FFP respectively. Preoperative management, anaesthetic and surgical techniques will be standardized for both groups.

Primary and Secondary Outcome Measures: The primary outcome is the volume of blood loss during and within 24 hours after surgery. The secondary outcomes include (1) the total units of allogeneic red blood cells (RBCs) transfused during and within 7 days after surgery, (2) re-exploration due to postoperative bleeding within 7 days after surgery, (3) adverse events and serious adverse events (SAE) within 30 days after surgery, and (4) length of intensive care unit (ICU) stay and hospital stay.

Trial registration: Registered under NCT04244981 at ClinicalTrials.gov on 28 January 2020, https://clinicaltrials.gov/ct2/show/NCT04244981?cond=NCT04244981&draw=2&rank=1.

Ethics and dissemination: This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (ZS-2242).

Key words: prothrombin complex concentrate, fresh frozen plasma, perioperative blood loss, cardiac surgery, cardiopulmonary bypass

Strengths and Limitations:

- This study focuses on the efficacy of prothrombin complex concentrate (PCC), compared with fresh frozen plasma (FFP), in reducing perioperative blood loss under cardiopulmonary bypass in cardiac surgery.
- Considering the insufficiency and disadvantages of FFP, the study may provide an alternative strategy for the treatment of major blood loss in cardiac surgery.
- The limitation in this study is that the doses and time of intervention are based on guidelines and clinical practice, not having previous evidence in our own research team to provide stronger support.

INTRODUCTION

Major bleeding and allogeneic blood transfusion are major complications of cardiac surgery[1,2], with increased risk of serious postoperative morbidities including infections, atrial fibrillation, respiratory complications, acute kidney injury, short-term and long-term mortality, and increased medical costs[3-5]. Compared to all other surgeries, cardiac surgery is among the highest overall rate of RBC transfusion, accounting for 10%-15% of all RBC transfusions in the United States and the United Kingdom[6,7]. Approximately 10% of all cardiac surgery patients suffer from severe or massive blood loss, and up to 5% require emergent re-exploration in an attempt to correct ongoing bleeding and establish adequate hemostasis[8,9].

Coagulopathy is one of the main reasons for massive perioperative bleeding and allogeneic blood transfusion in cardiac surgery and cardiopulmonary bypass (CPB)[10]. In addition to decreasing platelet and fibrinogen levels, coagulation factor deficiency also plays an important role in post-CPB coagulopathy[11]. Fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) are currently used primarily to treat perioperative coagulopathy in cardiac surgery[12] and suitable for increasing the concentration of vitamin K-dependent coagulation factors. FFP has been widely used to acutely treat coagulopathy in the past decades, which contains all of the necessary clotting factors and also fibrinogen[13]. Compared with FFP, PCC offers several advantages in the management of cardiac surgery coagulopathy, such as faster infusion rates, lower volume overload, shorter preparation time, no blood-type matching needed, and lower rate of transfusion reaction[14]. In addition, in many hospitals in our country, FFP that blood banks could provide in time is always insufficient in clinical practice and often cannot meet the treatment demands of perioperative bleeding and coagulation dysfunction. Therefore, we hope to gradually reduce the use of FFP and switch to use PCC to treat perioperative coagulopathy in cardiac surgery.

A body of evidence have suggested that PCCs can provide more rapid and effective treatment for warfarin and vitamin K antagonists (VKA) reversal compared with FFP, with rapid international normalized ratio (INR) correction and greater increase in clotting factors[15-17]. However, there are only a few studies, mostly retrospective studies, concentrating on PCC for the treatment of post-CPB bleeding, which indicate that the use of PCC is associated with less chest tube output and red blood cell transfusion versus FFP[18-21]. Properly designed randomised controlled clinical trials (RCT) should be done to evaluate the efficacy and safety of PCC compared with FFP.

Considering the gap, we want to design an RCT to identify the efficacy of PCC compared with FFP in the treatment for coagulopathy in cardiac surgery, exploring whether PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB.

METHODS

Study design

This is a non-inferiority, randomised controlled clinical trial. The trial will be conducted at the National Center for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital, China. A total of 594 participants will be randomised. The trial schema is shown in Figure 1, and the study period is shown in Figure 2. The study will be monitored by an independent Trial Steering Committee and Data Safety Monitoring Committee.

Study population

Inclusion criteria

Eligible patients must meet all of the following criteria:

1. Age between 18 and 80 years.
2. Undergoing elective coronary artery bypass grafting (CABG) or valve replacement or valvuloplasty through CPB.

3. Developing coagulation factor deficiency or coagulopathic bleeding during the surgery, meeting the indications of PCC or FFP treatment.
4. Signing of the informed consent form.

Exclusion criteria

The exclusion criteria are as follows:

1. History of cardiac surgery.
2. Hepatic dysfunction before surgery.
3. Coagulopathy before surgery, including inherited or acquired coagulation factor deficiencies, thrombocytopenia, platelet dysfunction and other bleeding disorders.
4. Use of warfarin within three days and direct oral anticoagulants within 48 hours (or 72 hours if patient has renal impairment) before surgery.
5. Withdrawal of clopidogrel or aspirin less than 7 days and low molecular weight heparin less than 24 hours before surgery.
6. Allergy to allogeneic blood products.
7. Pregnancy.
8. Other serious diseases that may affect patient survival time, such as cancers.

Randomisation and blinding

Stratified randomisation will be used to assign the patients to two groups. The informed consents of those patients meeting the admission criteria will be obtained before surgery. Then patients will be randomly assigned to 2 groups by a specific computer randomisation system, when at least one of the following criteria is met: a) INR > 1.7 measured 20 minutes after CPB, b) prolonged PT or APTT (> 1.5 times baseline) measured 20 minutes after CPB, and c) excessive bleeding observed. Nurse anaesthetists will prepare the corresponding products for each patient according to the group assignments in an anaesthesia preparation room. PCC or FFP will be pumped into 50 ml syringes firstly, covered with opaque paper to hide the contents. For group PCC, we first diluted PCC to 50ml with normal saline, and then supplemented subsequent volume using normal saline to make it equal to the corresponding required

volume of FFP. The enrolment number of each patient will be marked on the syringes. Finally, the corresponding interventional products will be given to patients from syringes, followed by the light-protected infusion set. Participants, anaesthesiologists, surgeons, and outcome assessors will all be blinded to the group assignments throughout the trial. In the case of the need for emergency rescue, if it is necessary to know the intervention for a participant, blinding will be broken. The allocation will be disclosed to healthcare providers in case of emergency in compliance with ethics considerations.

Interventions

Participants will be randomly assigned to 2 groups named the prothrombin complex concentrate group (group PCC) and the fresh frozen plasma group (control group or group FFP) respectively, with 297 cases in each group.

Preoperative management, anaesthetic and surgical techniques will be standardized for all patients. Various demographic as well as preoperative physiological and laboratory parameters will be recorded for each patient. During the operation, all patients will be under general anaesthesia. The surgical procedures will be performed through a median sternotomy approach, and CPB will be undertaken in a standardized fashion. A mild hypothermia condition (32-34℃) will be achieved, and heparin (400 IU/kg) will be intravenously administered before initiation of CPB, with activated clotting time (ACT) maintained above 480 seconds during CPB. In addition, tranexamic acid will be intravenously administered after the induction of anaesthesia until the end of the operation (20 mg/kg for the first hour and 2 mg/kg thereafter). After CPB, circulating heparin will be antagonized with protamine sulfate at a ratio of 1 mg of protamine per 100 IU of heparin, making ACT within 130 s. Prolonged ACT will be treated with an additional dose of protamine sulfate. The cell saver machine will be used during surgery, and the following parameters should be checked and corrected off bypass as necessary: (1) patient's core temperature, (2) arterial blood gases (ABGs), (3) post CPB coagulation screening results: a) the platelet count, b) the international normalized ratio

(INR), c) the activated partial thromboplastin time (APTT) and prothrombin time (PT) and d) serum fibrinogen levels. Off bypass, all patients' core temperatures will be raised above 37℃.

PCC or FFP will be transfused when coagulation factor deficiency or coagulopathic bleeding is observed. In this study, the indications of PCC or FFP treatment include INR > 1.7 or prolonged PT or APTT (> 1.5 times baseline) measured 20 minutes off-pump (ACT within 130 s), or excessive bleeding observed during the surgery[22-24]. In the presence of these conditions, 4-factor PCC (15 IU/kg) or FFP (10 mL/kg) will be given according to the group assignments, guided by manufacturer's instructions and previous research[22]. Half an hour after transfusion, the re-evaluation will be done and an additional dose will be administered if required. Other allogeneic blood products will be needed if cell saver is insufficient for patients, and transfusion will be guided by the haemoglobin concentration, the platelet count, the INR, the PT, the APTT and serum fibrinogen levels. Homologous red blood cells (RBCs) will be intraoperatively administered to maintain a haemoglobin concentration > 7 g/dl or a haematocrit higher than 20%. Platelets will be transfused when their count is $\leq 60\times10^9$/l. Serum fibrinogen levels less than 1.5 g/l will be corrected with fibrinogen concentrate at doses of 25-50 mg/kg. Additional blood product transfusions also will be performed at the discretion of the clinical team in the operating room.

After surgery, patients will be sent to the intensive care unit (ICU) and then back to the ward after their conditions stable. Patients' haemoglobin concentrations, haematocrit levels, platelet counts, INRs, PTs, APTTs, fibrinogen levels and blood biochemistry parameters will be monitored daily in the ICU. RBCs will be transfused if the haemoglobin concentration is ≤ 7 g/dl. Other blood product transfusions will be performed at the discretion of critical care physicians and surgeons based on patient conditions and laboratory test results.

Researchers who deliver the PCC or FFP to participants during the surgery will receive specific training to guarantee that the interventions are provided according to the

randomised groups. The anaesthesia records, medical records and medical orders will be reviewed to confirm the interventions.

Follow-up and withdrawal

The study follow-up is scheduled as 24, 48, 72 hours and 7 days after surgery, or discharge or death, whichever is first, to record observations relevant to the study and the results of laboratory testing. The laboratory tests will include the haemoglobin concentration, hematocrit level, platelet count, INR, PT, APTT, fibrinogen level, and blood biochemistry parameters such as creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) concentrations. Blood loss will be recorded during the surgical procedure and within 24 hours after surgery. Other examinations will include electrocardiography, X-ray, and echocardiography. Adverse events and serious adverse events (SAE) will be followed and collected within 30 days after surgery or death, whichever is first. EpiData Software will be used for data entry and storage. Double data entry will be used to ensure data quality.

Every reasonable effort will be made to maintain protocol compliance and retain patient participation in the study. Participation will be terminated if the patient withdraws from the study. A study withdrawal form will be completed for these patients, and the reason for withdrawal will be captured. All subjects withdrawn from the study will be managed in accordance with the hospital's standard procedures.

Outcomes

Primary outcome

The primary outcome is the volume of blood loss during and within 24 hours after surgery.

Secondary outcomes

The secondary outcomes include (1) the total units of allogeneic RBCs transfused during and within 7 days after surgery, (2) re-exploration due to postoperative bleeding within 7 days after surgery, (3) adverse events and SAEs within 30 days after surgery, and (4) length of intensive care unit (ICU) stay and hospital stay.

Intraoperative blood loss will be assessed by measuring the amount collected by aspiration and weighing the surgical gauze compresses. Blood loss from the floor, surgical gowns and surgical drapes are not included. Postoperative blood loss will be recorded as the blood volume collected through the suction drains at 24 hours.

Statistical analysis

Sample size

This is a clinical non-inferiority trial based on the hypothesis that PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB. According to previous studies in our research team, the mean volume of blood loss during and within 24 hours after cardiac surgery under CPB is 726.3 ml, and the standard deviation is 824.38 ml. A non-inferiority margin is set at 200 ml based on clinical practice. To achieve 80% power at the 2.5% significance level, a sample size of 267 patients for each group is needed. Considering a 10% dropout rate, a total of 594 patients (297 per group) is necessary.

Statistical methods

Modified intent-to-treat analysis will be used for all valid variables. All randomised subjects in the study, regardless of adherence to the study process or whether an adverse event occurs before or after the intervention, should be included in the analysis. Sensitivity analysis will be performed to assess the bias that may be introduced due to nonadherence to the protocol or missing data. Baseline characteristics will be tabulated and compared between the PCC and FFP groups using standardized differences, and a value larger than 0.2 will be regarded as a clinically relevant difference between groups. The primary outcome, the volume of blood loss during and within 24 hours after surgery, will be compared using the t-test with log transformation of the variable. Continuous secondary outcomes and the total units of allogeneic RBCs transfused during and within 7 days after surgery will be compared using a t-test with log transformation of the variable. The rate of re-exploration due to bleeding within 7 days after surgery will be compared using the chi-square test. Treatment effect will be measured by odds ratio

and mean difference for binary and continuous outcomes with corresponding 95% confidence intervals. No correction for multiple comparisons will be conducted in the analysis of the secondary outcomes; hence, the findings for secondary outcomes will be interpreted only as explanatory results. For safety outcomes, we will only describe the incidence of overall adverse events, SAEs, and component adverse events without statistical tests between two groups. A two-sided P-value < 0.05 was considered indicative of statistical significance.

Adverse events

Adverse events are defined as any undesirable event occurring in a patient during the study regardless of whether the event is considered to be related to PCC or FFP, such as thromboembolic events (including arterial and venous), perioperative myocardial infarction, renal dysfunction, hepatic dysfunction and neurological complications. All adverse events reported spontaneously by the patient or observed by the investigator or staff will be recorded and should be judged for relevance to the study intervention by researchers. A detailed description should be made and recorded in the summary report, including the date, manifestations, laboratory results, classification (Table 1) and prognosis (Table 2).

SAE is defined as any untoward medical occurrence or effect that results in death, is life-threatening (at the time of the event), requires hospitalization or prolongs length of hospital stay, or results in persistent or significant disability or incapacity, or any other important medical event that does not result in any of the outcomes listed above due to medical or surgical intervention but could be based upon appropriate judgement by the investigator. Any SAE should be recorded on the case report form (CRF). SAEs that occur from the beginning of the study to 24 hours after surgery should be reported to the Ethics Committee within 24 hours, even if it may not be associated with the study regimen. The related follow-up data should be reported to the sponsor after 24 hours.

Protocol amendments

The current protocol is version 3.0, date 2021-9-21. Any changes in the protocol during the trial that may affect the conduct of the trial, the safety and the benefit to patients will require a formal amendment to the protocol.

Patient and public involvement

This research will be done without patient involvement. Patients will not be invited to comment on the study design or contribute to the acquisition, analysis, or interpretation of data for the work. Patients will not be consulted to develop relevant outcomes. Patients will not be invited to draft the manuscript for integrity or accuracy.

DISCUSSION

Coagulopathy is an important risk factor for bleeding and blood transfusion in patients undergoing cardiac surgery, associated with both early and late morbidity. Administration of FFP and PCC is current treatment regimens for clotting factor deficiency, which might be one of the major reasons of coagulopathy after CPB during cardiac surgery[14]. Considering the advantages of PCC over FFP[25-27] and the insufficiency of FFP in clinical practice setting, more and more research has been conducted to explore the efficacy and safety of PCC versus FFP in various conditions[28,29]. Till now, the use of PCC is recommended highly for severe bleeding from warfarin, as well as for patients undergoing urgent surgery or invasive procedures based on guidelines from several organizations[23,24,30].

However, for perioperative bleeding and prolonged clotting times during cardiac surgery, the data are very limited. Several retrospective studies showed less perioperative bleeding and blood transfusion in patients with PCC, compared with FFP. In an observational study by Cappabianca et al[18], when 3-factor PCC was administered prior to chest closure or in the first few postoperative hours as a first-line treatment for post-CPB bleeding, there were less chest tube output and red cell transfusion versus FFP. In a retrospective cohort study, Arnekian et al[31] showed that low-dose PCC (10 U/kg) was associated with reduced blood loss during the initial hours after cardiac surgery. Patients who received combined FFP and PCC underwent more re-

explorations than other groups. Clinical validation studies, such as properly designed RCTs still are needed to provide stronger evidence. So this time, we designed this non-inferiority, randomised controlled clinical trial to explore the efficacy of PCC, compare with FFP, for the treatment of perioperative blood loss during general cardiac surgery.

In our study, we will choose the patients undergoing elective CABG, valve replacement or valvuloplasty through CPB in National Centre for Cardiovascular Diseases, Fu Wai Hospital, and Peking Union Medical College Hospital, China. Both hospitals are top medical institutions in China, with a large number of patients and standardized clinical diagnosis and treatment strategies, ensuring the feasibility and reliability of this study.

After obtaining the informed consents, patients meeting the administration criteria will be pre-enrolled and then actually enrolled and randomised into different groups (group PCC or group FFP) when meeting the indications of PCC or FFP treatment. According to guidelines and previous research, such indications include INR > 1.7, prolonged PT or APTT (> 1.5 times baseline), or excessive bleeding observed during the surgery[22-24]. In other words, any symptoms reflecting the coagulation factor deficiency or coagulopathic bleeding during the surgery will trigger the transfusion of PCC or FFP.

The recommended dose of PCC in guidelines is mainly used to reverse the effects of VKA and correct INR[16,24,31], which is not quite suitable for our study. Patients included in our study will undergo non-complex cardiac surgery and will not be on anticoagulation therapy prior to surgery, so they rarely develop INR > 2 and require such high level of PCC[32]. To choose the proper dose of PCC, we firstly selected 10 mL/kg for FFP according to the guidelines[23,24], previous research[22] and clinical practice. Then taking the dose balance of two intervention products, previous research which included similar patients as our study[22], and the manufacturer's instructions of PCC used in this study into consideration, we finally chose 15 IU/kg for PCC.

The primary safety concern with PCCs has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation and deep vein thrombosis[33]. A meta-analysis of 27 clinical

studies involving 1,032 patients presenting with bleeding or undergoing surgery showed that emergency reversal of warfarin with PCC was associated with a 1.4% incidence of thromboembolic events. The incidence was 1.8% with 4-factor PCC (20 studies) and 0.7% with 3-factor PCC (7 studies), with a mortality rate of 10.6%[34]. Although these events were associated with PCC administration, they could be attributed to the patients' underlying thrombotic risk factors in most cases. In addition, the already low incidence of such adverse events has further decreased over the last few years due to improvements in the composition of the more recent commercially available PCC (i.e., inclusion of coagulation inhibitors, reduced use of activated coagulation factors, and improved balance of coagulation factors). Current evidence suggests that thromboembolic events and mortality are not increased with the use of PCCs[14].

Our study also has several limitations. This is an exploratory study without pilot study before. The doses and time of intervention are based on guidelines and clinical practice, not having previous evidence in our own research team to provide stronger support. Further clinical validation studies for doses and time of PCC administration are needed to establish the most effective and safe way of administering PCC to cardiac surgical patients.

In conclusion, this study aims to identify the efficacy of PCC compared with FFP, exploring whether PCC is not inferior to FFP in reducing perioperative blood loss in patients undergoing cardiac surgery under CPB. Considering the gap of current research, our study will provide stronger clinical evidence and data support for PCC treatment in perioperative coagulopathy bleeding during general cardiac surgery, and also provide reference and guidance for clinicians in perioperative blood management during cardiopulmonary bypass.

DECLARATIONS

Consent for publication

Consent for publication will be obtained.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Access to data

The sponsor of this study, also the corresponding author, and the authorized data analyst will have access to the final trial dataset.

Confidentiality

Only the ID and clinical data of participants will be recorded on the CRF, and no specific personal information will be retained. ID numbers will be encoded to protect confidentiality.

Competing interests

The authors declare that they have no competing interests.

Funding

This research will be supported by Peking Union Medical College Hospital Precipitation and Integration Foundation (ZC201906511). The funders had neither role in the design of the study, collection, analysis, interpretation of data, nor in writing the manuscript.

Trials status

This protocol is version 3.0, date 2021-9-21. The recruitment is planned to begin on January 1st, 2022, and end on December 31st, 2024, lasting 3 years.

Author contributions

Lijian Pei, Chen Sun and Jia Shi participated in the design and coordination of the study. Chen Sun, Lijian Pei, Hong Lv, Yuelun Zhang and Jia Shi collected references and developed the protocol. Chen Sun, Jia Shi and Yuelun Zhang performed the statistical

analysis. Lijian Pei, Chen Sun and Jia Shi drafted the manuscript. All authors read and approved the final manuscript.

Lijian Pei and Chen Sun contributed equally to the work.

Acknowledgements

Not applicable.

Ethics and dissemination

This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (ZS-2242). Written informed consent will be obtained from all subjects involved.

Exclusive license statement

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413 above.

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Table 1 Classification of adverse events

Classification	Definition
Mild	With manifestations but no limitation of physical activity
Moderate	With limitation of physical activity
Severe	Unable to carry on any physical activity

Table 2 Prognosis of adverse events

Prognosis	Definition
D	Death
P	Permanent or organic labor loss
H	Hospitalization
N	None of the above

Figure 1 Study design and participant flow chart

Figure 2 Study period

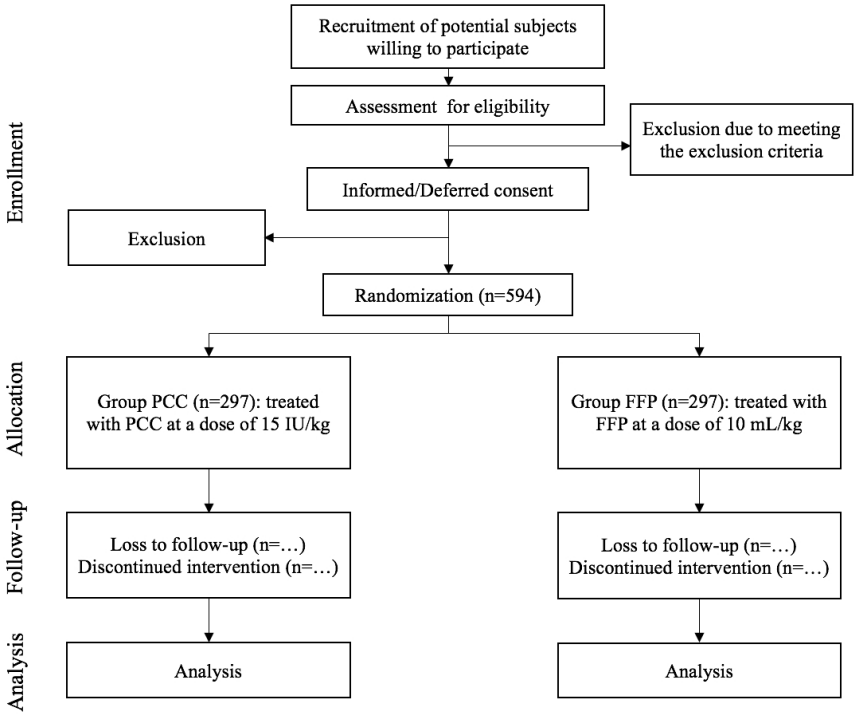

Figure 1: Study design and participant flow chart

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	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				Close-out
TIMEPOINT	***Within 7d before surgery***	***1d before surgery***	***1h before surgery***	***Intra-operation***	***24h after surgery***	***48h after surgery***	***72h after surgery***	***7d after surgery***
ENROLMENT:								
Eligibility screen		X						
Informed consent		X						
ALLOCATION:			X					
INTERVENTIONS:								
PCC				X				
FFP				X				
ASSESSMENTS:								
Baseline variables:								
Hb	X			X	X	X	X	
Hct	X			X	X	X	X	
Plt	X			X	X	X	X	
INR	X			X	X	X	X	
PT	X			X	X	X	X	
APTT	X			X	X	X	X	
Fibrinogen	X			X	X	X	X	
Blood biochemistry	X			X	X	X	X	
Outcome variables:								
Blood loss				X	X			
RBC transfusion				X	X	X	X	X
Re-exploration					X	X	X	X

Figure 2: Study period

561x519mm (57 x 57 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Trial registration, Page 2)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Yes.)**
Protocol version	3	Date and version identifier **(Page 1)**
Funding	4	Sources and types of financial, material, and other support **(Funding, Page 14)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Affiliation, Author's Contributions, Page 1, 14)**
	5b	Name and contact information for the trial sponsor **(Corresponding author, Page 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 **(N/A. No sponsor and funders in this study.)**
	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) **(Study design, Page 4)**
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 **(Introduction, Page 3)**
	6b	Explanation for choice of comparators **(Randomization and blinding, Page 5-6)**
Objectives	7	Specific objectives or hypotheses **(Page 4)**

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) **(Study design, Page 4)**

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 **(Study design, Page 4)**
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) **(Inclusion criteria, Exclusion criteria, Page 4-5)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Interventions, Page 6-7)**
	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) **(Follow-up and withdrawal, Page 8)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Interventions, Page 6-7).**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A. There is no special relevant concomitant care and interventions that are permitted or prohibited during the trial.)**
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 **(Outcomes, Page 8-9)**
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) **(Figure 1, in Attach Files)**
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 **(Sample size, Page 9)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Study design, Inclusion criteria, Exclusion criteria, Page 4-5)**

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 **(Randomization and blinding, Page 5-6)**
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 **(Randomization and blinding, Page 5-6)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Randomization and blinding, Page 5-6)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(Randomization and blinding, Page 5-6)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(Randomization and blinding, Page 5-6)**
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 **(Follow-up and withdrawal, Page 8)**
	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 **(Follow-up and withdrawal, Page 8)**
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 **(Follow-up and withdrawal, Page 8)**
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 **(Statistical methods, Page 9)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A.There isn't any additional analyses.)**

	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) **(Statistical methods, Page 9)**
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 **(N/A. This study focuses on the perioperative period which lasts for no more than 7 days after surgery, and there won't be too many data collected in the study, so it is not necessary to develop a DMC.)**
	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 **(N/A. Interim analyse is not applicable to this study.)**
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 **(Adverse events, Page 10)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(N/A. There is no auditing trial conduct.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Ethics and dissemination, Page 15)**
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) **(Protocol amendments, Page 10-11)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Ethics and dissemination, Page 15)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A. No additional consent provisions in this study.)**
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 **(Confidentiality, Page 14)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Consent for publication, Funding, Page 14)**

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 **(Access to data, Page 14)**
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 **(N/A. No provision 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 **(N/A. No plan for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups.)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A. There is no authorship eligibility guidelines and any intended use of professional writers.)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(N/A. No plan 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 **(Informed consent, Appendices)**
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 **(N/A. No biological specimens were collected as part of this trial.)**

*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.