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Protocol for a multicentre, randomised, parallel-control, superiority trial comparing administration of clotting factor concentrates with a standard massive haemorrhage protocol in severely bleeding trauma patients: the FiiRST 2 trial (a 2020 EAST multicentre trial)

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ABSTRACT

Introduction Acute traumatic coagulopathy (ATC) in bleeding trauma patients increase in-hospital mortality. Fibrinogen concentrate (FC) and prothrombin complex concentrate (PCC) are two purified concentrates of clotting factors that have been used to treat ATC. However, there is a knowledge gap on their use compared with the standard of care, the transfusion of plasma.

Methods and analysis The factors in the initial resuscitation of severe trauma 2 trial is a multicentre, randomised, parallel-control, single-blinded, phase IV superiority trial. The study aims to address efficacy and safety of the early use of FC and PCC compared with a plasma-based resuscitation. Adult trauma patients requiring massive haemorrhage protocol activation on hospital arrival will receive FC 4 g and PCC 2000 IU or plasma 4 U, based on random allocation. The primary outcome is a composite of the cumulative number of all units of red cells, plasma and platelets transfused within 24 hours following admission. Secondary outcomes include measures of efficacy and safety of the intervention. Enrolment of 350 patients will provide an initial power >80% to demonstrate superiority for the primary outcome. After enrolment of 120 patients, a preplanned adaptive interim analysis will be conducted to reassess assumptions, check for early superiority demonstration or reassess the sample size for remainder of the study.

Ethics and dissemination The study has been approved by local and provincial research ethics boards and will be conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines and regulatory requirements. As per the Tri-Council Policy Statement, patient consent will be deferred due to the emergency nature of the interventions. If superiority is established, results will have a major impact on clinical practice by reducing exposure to non-virally inactivated blood products, shortening the time for administration of clotting factors, correct coagulopathy more efficaciously and reduce the reliance on AB plasma.

Trial registration number NCT04534751, pre results.

Strengths and limitations of this study

- This is the first large randomised controlled trial assessing the early preemptive coadministration of fibrinogen concentrate and prothrombin complex concentrate for haemorrhaging trauma patients.
- The trial is the first one to compare the use of both investigational products with the standard of care, the replacement of clotting factors with a ratio-based plasma resuscitation.
- The use of an active control will permit that all patients receive clotting factors supplementation as clinically indicated.
- Clinicians will not be fully blinded to treatment allocation. However, patients, caregivers, clinical team members involved in care after trauma bay resuscitation and all outcome assessors will be blinded to minimise risk of bias.
- The study design aligns with standard clinical practice which will permit and enhance adherence and ensure clinical relevance and generalisability, while stratified randomisation by participating site is applied to address between-site practice variability.

INTRODUCTION

After hospital arrival, the most common cause of death in trauma patients is uncontrolled

or refractory haemorrhage aggravated by acute trauma coagulopathy (ATC), which is present in up to 25% of all trauma patients and 100% of severely injured patients.[1] ATC is multifactorial, caused by clotting factor deficiencies, hypofibrinogenemia, hyperfibrinolysis and platelet and endothelial dysfunction.[1] ATC is part of the 'lethal triad' of coagulopathy, acidosis and hypothermia. Despite knowledge that the lethal triad must be avoided and, where present, addressed promptly, different strategies to correct ATC have not been addressed in definitive clinical trials. Trauma patients with ATC have a threefold greater in-hospital mortality and are more likely to experience early haemorrhagic death in the first 24 hours.[2–5] ATC is also associated with higher transfusion requirements and multiorgan dysfunction, as well as longer duration of mechanical ventilation, intensive care unit (ICU) stay and hospital stay.[6]

In North America, ATC is typically treated with ratio-based plasma resuscitation, where 1 unit of frozen plasma (FP) is transfused for every 1–2 red blood cell (RBC) units until haemorrhage is controlled and blood components can be administered based on coagulation test results.[7] In contrast, in many European countries, fibrinogen concentrate (FC) and prothrombin complex concentrates (PCCs) are administered instead of FP.[8] The FC +PCC strategy has several potential advantages compared with plasma: simplified logistics by reducing the door-to-needle time (no knowledge of blood group needed, no thawing of FP, convenience of storage at room temperature where needed and ability to safely administer during transport from remote geographic regions), a reduced risk of some transfusion reactions and pathogen transmission (FC and PCC are pathogen-inactivated protecting patients from emerging pathogens) and an elimination of the need for reserving AB plasma for trauma patients. In contrast, the current standard of care (FP) may be theoretically superior due to the additional volume administered in this hypotensive population and replacement of clotting factors that are not present in the FC/PCC products. However, there are little data to support the use of FP in general due to the paucity of trials as concluded by a recent Cochrane systematic review.[9] Moreover, in a single, small trial[10] in Europe that compared these two strategies, the FC +PCC strategy was found to be superior, with a reduction in the need for massive transfusion (>10 units of RBC) and more rapid correction of coagulopathy. This study, however, does not resolve the lack of definitive knowledge. Confirmatory trials are needed.

Use of FC in trauma patients has been described in small studies.[11–13] Four systematic reviews[14–17] have addressed feasibility, efficacy and safety regarding the use of FC in trauma and other settings. These small studies demonstrate that FC improves coagulation and decreases the number of allogeneic blood products (ABPs) transfused, including RBCs, FP and platelets, without identifying any safety concerns such as thromboembolic (TE) complications. Similarly, the use of PCC as an alternative source of clotting factors (as compared with FP) has been investigated in other small studies,[10 18–20] which reported a decreased number of ABP units transfused and improved coagulation assays, again without safety concerns. Recently, a meta-analysis[21] of coagulopathic patients who were not receiving anticoagulants reported that a resuscitation strategy using both PCC and plasma was associated with reduced mortality in a subpopulation of trauma patients, when compared with plasma alone. In the same study, PCC use compared with strategies not involving PCC reduced the need for RBC transfusions. Furthermore, no risk of TE events was increased in the whole cohort. However, the efficacy and safety of early replacement of FC and PCC as a source of fibrinogen and clotting factors in bleeding trauma patients has yet to be demonstrated in a definitive large multicentre, randomised trial.

The Factors in initial Resuscitation of Severe Trauma 2 (FiiRST 2) trial will determine the impact of FC and PCC used together as an early hemostatic therapy in bleeding trauma patients, as compared with the standard massive haemorrhage protocols (MHP) that infuse 1 FP unit for every 1 or 2 RBC units. This trial will provide efficacy data on the number of ABPs transfused, coagulation tests and clinical and safety endpoints.

METHODS AND ANALYSIS

Objective

The primary objective of this randomised controlled trial is to demonstrate that the early coadministration of FC and PCC (Fibryga and Octaplex, respectively—Octapharma AG, Lachen, Switzerland) is superior to the current standard of care of ratio-based plasma resuscitation in severely injured trauma patients for whom an MHP is activated on admission to the emergency department (ED) in reducing the number of ABPs transfused in the first 24 hours.

Study design and setting

The FiiRST 2 trial is a phase IV, multicentre, randomised, controlled, superiority trial that uses a conventional, parallel group, two-armed, adaptive two-stage design and will be performed at eight level 1 trauma centres in Canada. It is preceded by a pilot randomised trial confirming the ability to randomise patients to the treatment arms and to administer FC within 1 hour of patient arrival to the trauma bay.[13] The study is designed to examine the effect of early replacement of fibrinogen and clotting factors via FC +PCC on the number of ABP units transfused within 24 hours following admission to the trauma bay/ED to trauma patients with severe haemorrhage versus the current standard of care, a ratio-based plasma resuscitation.

The study will aim to enrol 350 severely injured (penetrating or blunt) trauma patients at risk of significant haemorrhage for whom the institutional MHP has been activated within the first hour of arrival, according to local MHP activation criteria and/or judgement of the trauma

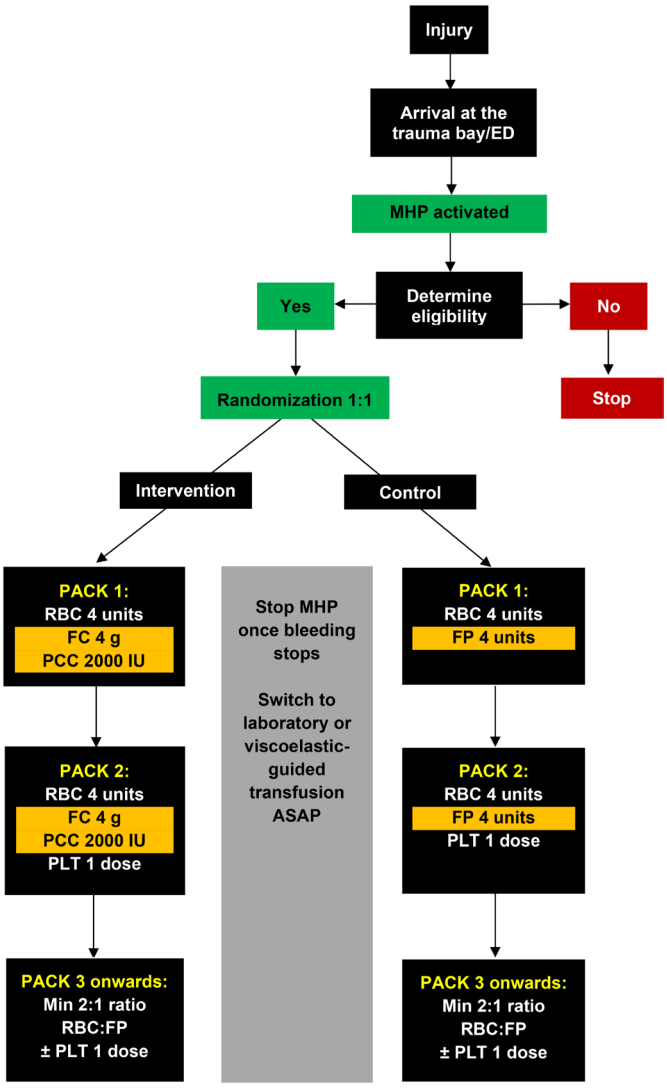

Figure 1 Study design. ED, emergency department; FC, fibrinogen concentrate; FP, frozen plasma; MHP, massive haemorrhage protocol; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cells.

team leader physician. Eligibility will be confirmed jointly by the trauma team and the blood bank technologist and eligible patients will be randomised to one of the two treatment groups. Patients will receive the treatment in MHP packs (figure 1). Patients in the intervention group will receive FC (Fibryga) and PCC (Octaplex) delivered in two MHP packs and patients in the control group will receive FP similarly delivered in two MHP packs.

Eligibility criteria

The study will enrol adult trauma patients (>16 years old) with blunt or penetrating injuries for whom an MHP is activated within the first hour following arrival to the trauma bay/ED. Patients will be excluded if they meet any of the following criteria: (1) Have received more than 2 U RBCs before admission (during transport or at transferring hospital); (2) have received more than 2 U RBCs in the trauma bay/ED before activation of the MHP; (3) have an elapsed time from injury of more than 3 hours (for patients with prolonged prehospital extraction or transport times); (4) have a penetrating traumatic brain injury with Glasgow Coma Scale of 3; (5) are known to be on anticoagulants in the last 7 days; (6) have known congenital or acquired bleeding disorder; (7) have a known pregnancy; (8) are known to have refused blood transfusion due to religious or other reasons and (9) have a known history of heparin-induced thrombocytopenia.

Intervention and control

Intervention

Each of the first two MHP packs given to patients in the intervention group will contain 4 g FC and 2000 IU PCC for coagulation factor replacement. Both products will be administered by slow intravenous injection, in the trauma bay/ED (each 1 g of FC over 1 min and each 1000 IU of PCC over 5 min). Products will be reconstituted at the bedside by the clinical team.

Active control

Patients randomised to the active control group will receive 4 U FP which will be released as part of the first and second MHP packs. In addition, FC may be administered if hypofibrinogenemia (fibrinogen level below 1.5–2.0 g/L or FIBTEM (fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D) A10 below 8–12 mm) is identified as part of routine testing, based on a specific order from the clinical team to the blood bank. All sites will maintain thawed AB or low titre group A plasma to eliminate delays in delivery of the FP. Patients in the control group will not be permitted to receive PCC during the intervention period (from admission to trauma bay/ED until when the two MHP packs are administered).

Procedures common to both groups

In both groups, 4 RBC units will be included as part of the first and second MHP packs, and 1 dose of platelets (pooled buffy coat 4-unit pools or 1 unit of apheresis platelet) will be included as part of the second MHP pack. The second MHP pack will be released at the request of the clinical team, but clinicians will be instructed to administer all the FC–PCC or FP in the first pack before transitioning to the second pack. Similarly, if the second pack is opened, clinicians will be instructed to administer all the FC–PCC or FP, before commencing transfusion of the coagulation contents of the third pack. Not administering all the investigational products in the first pack, once started, will be recorded as a protocol deviation. However, if all the investigational products are not completely administered when the second pack is opened, this will not be considered a protocol deviation.

The maximum time frame for administration of the second MHP pack (if required) is 24 hours from arrival at the trauma bay/ED or termination of the MHP (whichever comes first). If a third pack is required, and thereafter, patients in both groups will receive MHP packs according to MHP guidelines at each participating site

or revert to a laboratory or viscoelastic-guided transfusion as per the local guidelines if haemorrhage control is achieved and the MHP is terminated. All sites will terminate the MHP once bleeding is controlled and the criteria for MHP termination are met.

Administration of all non-investigational products will be at the discretion of the clinical team according to the haemodynamic status of the patient and/or laboratory or viscoelastic tests where available. While platelets will be routinely included in the second pack, clinicians can request platelets outside of the packs (eg, for patients on antiplatelet therapy or with marked thrombocytopenia on baseline testing).

An overview of the study design is presented in figure 1.

Outcomes and study duration

The primary outcome is one of efficacy; specifically, the comparison between study groups of the total number of all units of ABPs (RBCs, FP and platelets) transfused within 24 hours following arrival at the trauma bay/ED. Since over 85% of all platelets provided to the study sites will be 4-unit pools, all platelets administered will be numerically counted as four allogeneic exposures.

Secondary outcomes will include both efficacy and safety endpoints. For the former, the key secondary outcome is the number of units of RBCs transfused within the first 24 hours following arrival at the trauma bay/ED as a measure of haemorrhage control. Other additional efficacy endpoints include: (1) Total number of all units of RBCs, FP and platelets transfused within 24 hours following arrival at the trauma bay/ED excluding the FP units given as part of the active control (first two MHP packs); (2) total and individual numbers of units and volumes (litres) of ABPs (RBCs, FP and platelets) transfused within 6 hours and within 7 days post arrival at the trauma bay/ED; (3) total volume of crystalloids and other colloids administered within the first 6 hours and 24 hours following arrival at the trauma bay/ED; (4) rescue use of haemostatic agents (FC and recombinant factor VIIa) within the first 24 hours following arrival at the trauma bay/ED; (5) laboratory endpoints on arrival (before drug administration), if measured, and following infusion of the investigational medicinal products, as per each site protocol routine, measured within the first 24 hours and within 7 days following arrival at the trauma bay/ED; (6) percentage of patients who received calcium; (7) percentage of patients who received tranexamic acid; (8) ventilator-free days; (9) days out of hospital within the first 28 days following arrival at the trauma bay/ED; (10) time to death over the first 28 days following arrival at the trauma bay/ED and (11) cost-effectiveness with cost utility analysis and quality-adjusted life year of FC–PCC as compared with FP.

The key safety secondary outcome is incidence of TE events, as defined by evidence of any of the following, from arrival at the trauma bay/ED to up to 28 days: deep vein thrombosis, pulmonary embolism, myocardial infarction, ischaemic stroke and arterial or venous thrombosis at other sites. Safety endpoints include: (1) All documented adverse events (AEs) and serious AEs (SAEs) during the first 28 days following arrival, including multiorgan failure, abdominal compartment syndrome and limb compartment syndrome as defined by the medDRA classification system; (2) incidence of transfusion reactions as defined by the International Society of Blood Transfusion;[22] (3) incidence of treatment-emergent AEs; (4) duration of ICU stay and (5) 28-day all-cause mortality.

The duration of the treatment period is from randomisation to up to 24 hours. The maximum time for administration of the second MHP pack is 24 hours. If the second MHP is not initiated within the first 24 hours, the ABP units will not be added to the primary and secondary outcomes. The duration of the study for an individual patient is 28 days. The study was launched in April 2021 and will run for approximately 48 months.

Sample size

The sample size calculation was based on demonstrating superiority in efficacy of the intervention (FC +PCC) compared with the active control (FP), with respect to the primary outcome. To demonstrate that the early administration of FC–PCC is clinically superior to the usual component therapy, with respect to the primary outcome (mean number of ABP units within 24 hours post admission), a type I error probability of α=0.025 will be used. Inferences will be based on the one-sided 97.5% CI derived from the estimated least square means of a negative binomial regression model. Superiority will be concluded if the upper limit of this CI is less than 1.0 (ie, the mean number of ABPs is larger in the control group).

The superiority design of the FiiRST 2 trial was chosen due to the impact on clinical practice and logistical benefits that FC–PCC may offer. Empirical estimates of the mean number of ABP units within the first 24 hours and its dispersion were based on results of the FIIRST 1 Study.[11] In FiiRST 1, the mean (±SD) composite number of ABPs was 1.50 (±2.51) in the intervention group and 3.06 (±5.06) in the control group. A mean difference in 5 units of the composite outcome (eg, mean 15 units in the control group and mean 10 units in the intervention group) is considered as a clinically meaningful difference that should be detected with at least 80% power. This approach was used for power determination, which was calculated as 80% with a sample size of 297, which would suffice to demonstrate the superiority of the investigational treatment under the stated assumptions. The FIIRST 1 study had a 10% patient drop off (exclusions post randomisation for subjects where informed consent could not be obtained and for patients randomised and not treated with any coagulation products in pack 1). In addition, FiiRST 1 had 10% death rate. Hence, we inflated the sample size to account for a drop-out percentage by 15% for a final sample estimate of 350 patients.

Randomisation and blinding

This is a single-blinded randomised trial. Given that the products have different physical appearances and methods of administration, it is not possible to blind the treating clinicians to group assignment. The clinical team will remain blinded with a tamper-proof seal on the assigned products until the point of use. Caregivers and clinicians involved in patient care during the administration of the two first MHP packs will be trained not to register on paper or electronic notes the product names (FC, PCC, FP) administered to the patients. These procedures will be audited by the study monitors and feedback will be provided to the participating sites. In addition, patients, caregivers and clinical team members involved after the administration of the second pack and outcome assessors will remain blinded by using a generic product label in the patient chart.

Blinding of treatment will be performed by blood bank technologists. For the intervention group, FC and PCC will be placed in a tamper-sealed room temperature container and issued with the first set of RBCs and will be opened in the trauma bay/ED only immediately before infusion. Similarly, the control group will receive the standard MHP pack 1 in a tamper-proof cooler along with the first set of RBCs, which will only be opened immediately before transfusion.

The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial using a permuted-block, random allocation schedule. As transfusion practices are not standardised, randomisation will be stratified by study site. The random allocation schedule will be provided to participating centres in opaque, consecutively numbered envelopes. Neither the individual randomising nor any of the healthcare providers will know which treatment will be assigned to a given patient when the MHP pack is ordered.

Data analysis plan

Data collection and management

Data will be collected as part of the deferred consent up to the date the patient or substitute decision-maker expresses his/her desire to not participate. Table 1 illustrates full details of the data to be collected during the study, in addition to the timing and frequency of its collection. The investigator will ensure that the patient's confidentiality is preserved. All source records and source data will be maintained by the site investigator and preserved as stipulated by the regulatory authorities. An electronic data capture system will be used to collect study data. All patient information and data will be maintained as confidential and patients will only be identified using a sequential numbering system. The site investigator will maintain a confidential patient identification code list.

Statistical methods

In this randomised, active-control, superiority trial, statistical analysis of the primary efficacy outcome will be conducted according to modified intention-to-treat (mITT) principles. The mITT population will be comprised of randomised patients who receive any of the non-RBC products in MHP pack 1 or beyond of the intended first-line treatment up to the date the patient or the substitute decision-maker agrees to remain in the study after consent has been obtained. A secondary analysis will also be conducted for the per-protocol population, which excludes patients with major protocol deviations and patients who receive less than 50% of the coagulation factor replacement in pack 1. A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses by the sponsor/principal investigator (PI).

To demonstrate that the early coadministration of FC and PCC is clinically superior to the standard of care, with respect to the mean number of ABPs administered within 24 hours of arrival at the trauma bay/ED, a two-sample, one-sided test of the pair of hypotheses: H_0: RR $\geq RR_0$ versus H_a: RR $< RR_0$ will be carried out with a type I error probability of α=0.025. Here, λ_1 and λ_2 denote the mean number of ABPs (RBCs+FP+platelets) in the control group (standard of care) and intervention group, respectively, RR is the ratio λ_2/λ_1 and RR_0 will be set equal to 1.0 to test for superiority. Testing of the hypothesis will be performed in the context of a counting regression model (generalised linear model for count data with log-link function and a negative binomial error term[23]), with treatment group as main effect. Inferences will be based on the one-sided 97.5% CI for the ratio λ_2/λ_1 derived from the estimated least square means of this model. Superiority will be concluded if the upper limit of this CI is strictly less than R_0=1.0.

Other exploratory endpoints will also be examined in the efficacy analysis, such as: (1) Total number of all units of RBCs, FP and platelets transfused within 24 hours following arrival at the trauma bay/ED excluding the FP units given as part of the active control (first two MHP packs); (2) number of units of RBCs administered within 24 hours following trauma bay/ED admission; (3) total and individual number of units and volumes (in litres) of ABPs transfused within 6 hours and within 7 days post arrival at the trauma bay/ED. All these endpoints will be examined using point estimates with two-sided 95% CIs and descriptive statistics; (4) laboratory endpoints, including thromboelastometry measurements; (5) days out of hospital within the first 28 days following arrival at the trauma bay/ED and (6) time to death over the first 28 days following arrival at the trauma bay/ED.

Analyses of safety outcomes will be conducted in the safety analysis population which will include all randomised patients who receive any of the interventional products in the first MHP pack or beyond the intended first-line treatment and agree to remain in the study after consenting. Similarly, safety outcomes will be analysed analogously to the primary endpoint, presenting point

Table 1 Flow chart of study procedures and information collected at each study visit

Procedures	Visit 1 On arrival at the trauma bay/ED (day 0)	Visit 2 24 hours following arrival at the trauma bay/ED (day 1)	Visit 3 2–27 days following arrival at the trauma bay/ED	Visit 4 End of study visit: day 28 after arrival at the trauma bay/ED
Inclusion and exclusion criteria	x			
Randomisation	x			
Interventions administered		x		
Baseline data				
Demographics	x	x*		
Medical history	x	x*		
Prearrival medications	x	x*		
Injury data	x	x*		
Obtain deferred consent from SDM or patient if recovered		x	x	x
Primary endpoint				
Total composite units of RBC +FP+platelets		x (24 hours)		
Secondary endpoints				
Total number of units of RBCs		x (24 hours)		
Thromboembolic events†		x	x	x
Ventilator-free days				x
Additional endpoints				
Efficacy endpoints				
Total and individual numbers of units and volumes of ABPs (RBCs, FP, platelets) transfused		x (6 hours and 24 hours)	x (day 7)	
Total volume of crystalloids and other colloid use		x (6 hours and 24 hours)		
Rescue use of rFVIIa		x		
Total FC use		x		
Laboratory tests, including thrombelastometry measurements, where available		x	x (day 7)	
Days out of hospital within 28 days				x
Time to death				x
Safety endpoints				
AEs and SAEs		x	x	x
MOF (SOFA score)		x	x (daily)	x
ACS and LCS		x	x	x
Transfusion reactions from products transfused following arrival at the trauma bay/ED		x	x	x
Treatment-emergent events		x	x	x
Duration of ICU stay				x
All-cause mortality				x

*If not already collected.
†Including leg Doppler ultrasound or other imaging as per clinical indications.
ABP, allogeneic blood product; ACS, abdominal compartment syndrome; AEs, adverse events; ED, emergency department; FC, fibrinogen concentrate; FP, frozen plasma; ICU, intensive care unit; LCS, limb compartment syndrome; MOF, multiple organ failure; RBC, red blood cells; rFVIIa, recombinant factor VIIa; SAEs, serious AEs; SDM, substitute decision-maker; SOFA, sequential organ failure assessment.

estimates and two-sided 95% CIs in addition to descriptive statistics. Safety analyses will focus on treatment emergent AEs, defined as AEs that start or worsen after the start of treatment (intervention or active control group), such as: (1) Incidence of TE events; (2) ventilator-free days; (3) duration of ICU stay and (4) 28-day all-cause

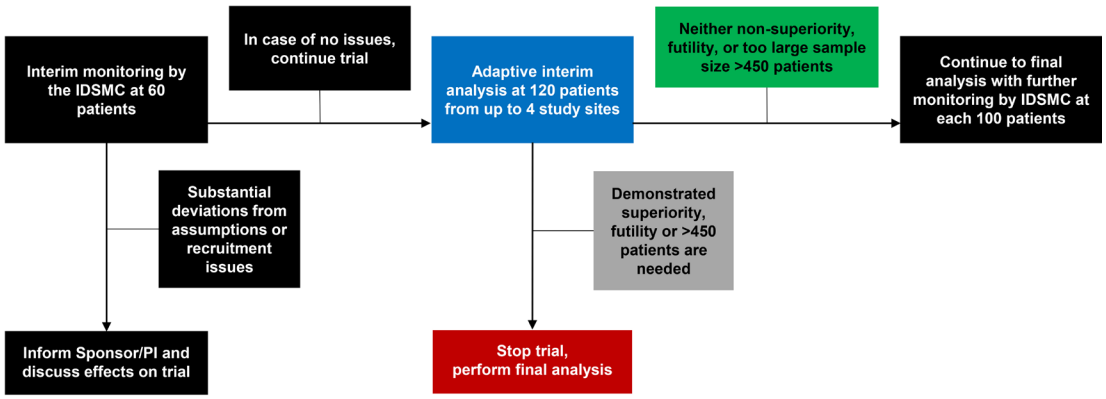

Figure 2 Study decision process at the point of the adaptive interim analysis. IDSMC, independent data safety monitoring committee; PI, principal investigator.

mortality. Patients who died will be summarised. Survival differences between treatment groups will be estimated by the risk ratio with 95% CI. Kaplan-Meier estimator for the time to death distribution will be calculated and graphically presented.

Due to the inherent variability in the primary endpoint and a yet substantial uncertainty about the effect size, an adaptive design approach will be used. For this, a single interim analysis will be performed after 120 patients have completed the study at up to four hospital sites. Primary aim of this interim analysis is to calculate the p value and conditional power of the test statistic for the primary endpoint and perform a sample size reassessment. This will be an unblinded interim analysis performed by an independent statistician who will report the results only to an independent data safety monitoring committee (IDSMC) which will make recommendations to the sponsor without revealing the treatment groups (figure 1). The study design will follow a group sequential design with Fleming *et al*'s error-spending function,[24] a futility boundary (conditional power less than 25%) and sample size re-estimation based on conditional power. Hence, the recommendation of the IDSMC can include: (1) To continue the trial as planned with the initial sample size; (2) to stop the trial for demonstrated superiority; (3) to stop the trial for futility; (4) to stop the trial for requiring an increase in sample size that is considered unfeasible (eg, total sample size larger than 450) or (5) to continue the trial with a modified sample size. Figure 2 describes the study decision process.

Cost-effectiveness analysis

A cost-effectiveness analysis to compare total costs and health outcomes of using FC+PCC compared with FP will be conducted. Costs and outcomes will be assessed within the 28-day trial period. Data on services used and the efficacy of FC+PCC will be captured. All costs will be calculated from a perspective of Canada's publicly healthcare system and expressed in 2020 Canadian dollars. The analysis will consider the following clinical outcomes: incidence of TE events, ventilation-free days, days spent at home within 28 days and 28-day all-cause mortality. The statistical analysis will be conducted in accordance with current guidelines for clinical and cost-effectiveness analysis alongside randomized controlled trials.[25] The incremental cost and incremental outcome will be estimated using generalised estimating equations that explicitly allow for the modelling of normal and non-normal distributional forms of repeated measure data.[26] We will estimate the following incremental cost-effectiveness ratios (ICERs): cost per one TE event case avoided, cost per one additional ventilation-free day, cost per one additional day spent at home and cost per one-life year saved. The ICERs will be obtained through the difference in the mean costs of the two strategies divided by the difference in the mean value of each clinical outcome as denoted by the coefficient of the therapy indicator variables. Uncertainty in the analysis will be addressed by estimating 95% CIs using a non-parametric bootstrapping method. For this study, we will obtain 5000 estimates of costs and outcomes for each strategy. Results from the bootstrapping exercise will also be used to depict cost-effectiveness acceptability curves, which shows the probability of a therapy being cost-effective over a range of potential threshold values that the health system may be willing to pay for an additional unit of effect.[27]

Monitoring and quality control and assurance

The IDSMC will be established by the sponsor/PI to review the data at the interim analysis of the adaptive interim phase, when 120 patients have been randomised, and subsequently at the enrolment of approximately each 100 patients. Additional unplanned meetings of the committee may be called based on the occurrence of SAEs, logistical issues or publication of evidence in other clinical trials. The results of the IDSMC meetings will be communicated to the sponsor/PI within 15 days or earlier in matters relating to ensuring patient safety and/or study integrity. The board will contain a minimum of three voting members with collective expertise in the fields of statistics, trauma and transfusion medicine, who will review accumulating data related to efficacy and safety outcomes and other study aspects such as compliance, recruitment, data quality and risk versus benefit.

The IDSMC will provide recommendations regarding continuation, modification or termination of the study, as appropriate. The role of the ISDMC members will be, ultimately, to protect and serve the study participants and to assist and advise the sponsor/PI in the overall conducts, interpretation, validity, integrity and ongoing relevance of the study. The responsibilities and duties of the IDSMC will be defined and described in a study-specific charter. The sponsor/PI will have the final authority in all aspects of the trial and will have full access to the final study dataset.

An independent study monitor will be nominated for quality control and assurance, periodic monitoring of study-related source data/records, adherence to the measures to maintain compliance with blinding, the approved protocol in general and completeness and accuracy of case report forms. Access to data source documents will be provided and all study-related material will also be available to the independent quality assurance auditors and regulatory inspectors, as required.

A steering committee will be created and will oversee the conduct of the trial in all its dimensions, thereby maximising the integrity of the data, and thus the validity of the results. The committee will include diverse clinical experts in haematology, pathology laboratory medicine, critical care, trauma, epidemiology, anaesthesiology, emergency medicine, blood transfusion services and clinical trials methodology. In addition, two patients will be part of the committee.

Patient and public involvement

A community consultation was performed for the pilot trial (13). An experienced social worker and case manager with vast experience in working with individuals of various ages, racial and cultural backgrounds after traumatic injury will be part of the steering committee. The steering committee will also have a patient representative who survived a penetrating trauma. The development of the research question and outcome measures were not informed by patients' priorities, experience or preferences. Patients were not involved in the development of study design, recruitment and study conduct and they did not assess the possible burden of the intervention.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki and in compliance with the approved study protocol, Good Clinical Practice guidelines and all appropriate regulatory requirements, including collecting and reporting SAEs. The study, study protocol and all other study documents have been approved by Sunnybrook Health Sciences Centre's (the coordinating centre) Research Ethics Board (REB) (REB no. 2031; approved on 3 September 2020), the local REB of all eight participating study sites and regulatory authority (Health Canada). Any protocol changes will be communicated by the sponsor/PI to all REBs, Health Canada, and will be registered on ClinicalTrials.gov.

This study will compare haemostatic therapies that are currently within the standard of care for trauma patients and poses no additional risks to patients and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (ie, patients experiencing massive haemorrhage), all eligible patients will be incapable of providing informed consent at the time the therapy and any delays in obtaining surrogate consent would be severely detrimental to their safety. Thus, we will employ a deferred informed consent approach.[25 26 28 29] We will obtain consent from the patient or a substitute decision-maker (SDM) as soon as possible after randomisation for ongoing collection and analysis of patient data. The investigator (or delegate as appropriate) will obtain freely given written consent from each patient (or SDM) after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the decision to continue to participate. The informed consent form must be signed, with name and date and time noted by the patient (or SDM), before the patient is exposed to any further study-related procedures, namely evaluation and data collection.

The PI (or delegate) will explain that the patients are completely free to withdraw from the study at any time, without any consequences for their further care and without the need to justify. Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

This consent process meets the criteria for alterations of the informed consent according to the Tri-Council Policy Statement for the ethical conduct for research involving humans: it involves a serious threat to the participants that requires immediate intervention, risk is not greater than that involved in standard efficacious care, participant is unconscious or lacks capacity to understand the risks, methods and purposes of the study and third party authorisation cannot be secured in sufficient time.

In accordance with the relevant guidelines, the sponsor/PI will prepare a clinical study report to report the outcomes of the study and may publish the data in their entirety as a multicentre dataset, at the completion of the study. We will disseminate the findings of the study in a timely fashion at local, national and international scientific meetings and will publish our findings in the scientific/medical literature.

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REFERENCES

1 Frith D, Brohi K. The pathophysiology of trauma-induced coagulopathy. *Curr Opin Crit Care* 2012;18:631–6.
2 MacLeod JBA, Lynn M, McKenney MG, *et al*. Early coagulopathy predicts mortality in trauma. *J Trauma* 2003;55:39–44.
3 Maegele M, Lefering R, Yucel N, *et al*. Early coagulopathy in multiple injury: an analysis from the German trauma registry on 8724 patients. *Injury* 2007;38:298–304.
4 Brohi K, Cohen MJ, Ganter MT, *et al*. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg* 2007;245:812–8.
5 Niles SE, McLaughlin DF, Perkins JG, *et al*. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma* 2008;64:1459–65.
6 Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. *Transfusion* 2014;54:1389–405.
7 Callum JL, Yeh CH, Petrosoniak A, *et al*. A regional massive hemorrhage protocol developed through a modified Delphi technique. *CMAJ Open* 2019;7:E546–61.
8 Spahn DR, Bouillon B, Cerny V, *et al*. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019;23:98.
9 Innerhofer P, Fries D, Mittermayr M, *et al*. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematol* 2017;4:e258–71.
10 Huber J, Stanworth SJ, Doree C, *et al*. Prophylactic plasma transfusion for patients without inherited bleeding disorders or anticoagulant use undergoing non-cardiac surgery or invasive procedures. *Cochrane Database Syst Rev* 2019;11:CD012745.
11 Curry N, Foley C, Wong H, *et al*. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Crit Care* 2018;22:164. 1.
12 Weiss G, Lison S, Glaser M, *et al*. Observational study of fibrinogen concentrate in massive hemorrhage: evaluation of a multicenter register. *Blood Coagul Fibrinolysis* 2011;22:727–34.
13 Nascimento B, Callum J, Tien H, *et al*. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. *Br J Anaesth* 2016;117:775–82.
14 Aubron C, Reade MC, Fraser JF, *et al*. Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review. *J Crit Care* 2014;29:471.e11–471.e17.
15 Kozek-Langenecker S, Sørensen B, Hess JR, *et al*. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care* 2011;15:R239. 1:R239.
16 Wikkelsø A, Lunde J, Johansen M, *et al*. Fibrinogen concentrate in bleeding patients. *Cochrane Database Syst Rev* 2013;8:CD008864.
17 Mengoli C, Franchini M, Marano G, *et al*. The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis. *Blood Transfus* 2017;15:318–24.
18 Schöchl H, Nienaber U, Hofer G, *et al*. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care* 2010;14:R55.
19 Schöchl H, Nienaber U, Maegele M, *et al*. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011;15:R83.
20 Schöchl H, Voelckel W, Grassetto A, *et al*. Practical application of point-of-care coagulation testing to guide treatment decisions in trauma. *J Trauma Acute Care Surg* 2013;74:1587–98.
21 van den Brink DP, Wirtz MR, Neto AS, *et al*. Effectiveness of prothrombin complex concentrate for the treatment of bleeding: a systematic review and meta-analysis. *J Thromb Haemost* 2020;18:2457–67.
22 International Society of Blood Transfusion Working Party on Haemovigilance. Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions, 2018. Available: https://www.isbtweb.org/fileadmin/user_upload/Proposed_definitions_2011_surveillance_non_infectious_adverse_reactions_haemovigilance_incl_TRALI_correction_2013_TACO_correction_2018.pdf [Accessed 9 Sep 2020].
23 Cameron AC, Trivedi PK. *Regression analysis of count data*. 1st edn. Cambridge, UK: Cambridge University Press, 1998.
24 Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. *Control Clin Trials* 1984;5:348–61.
25 Glick HA, Doshi JA, Sonnad SS, *et al*. *Economic evaluation in clinical trials*. University Press: Oxford, 2007.
26 Diggle P, Heagerty P, Liang K, *et al*. *Analysis of longitudinal data*. 2 ed. Oxford University Press, 2013: 400 p.
27 Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation for health care program*. University Press: Oxford, 2005.
28 Shaw D. HEAT-PPCI sheds light on consent in pragmatic trials. *The Lancet* 2014;384:1826–7.
29 Jansen TC, Kompanje EJO, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Crit Care Med* 2009;37:S65–8.