

Study of Whole blood in Frontline Trauma (SWiFT): Evidence of External Peer Review

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Research Code:	20/140
CI Name:	Dr. Laura Green and Prof. Jason Smith
Title of project proposal:	A randomised controlled trial of pre-hospital whole blood transfusion versus standard care for the resuscitation of patients with life-threatening haemorrhage.

Review

Please give an assessment of the strengths and weaknesses of the proposal, including your opinion regarding:

The current state-of-the-art in the field:

This is a definitive randomized controlled trial of pre-hospital whole blood as compared to the current standard of care, 2 RBC and 2 plasma units, in the UK pre-hospital air transport program. The study plans to enrol 844 patients with life-threatening bleeding in the prehospital setting who will undergo air transport to determine if this novel strategy reduces mortality at 30 days.

Strengths:

- 1) This is a very important question that needs to be answered before healthcare organizations adopt the use of whole blood in an evidence vacuum.
- 2) There are no other similar sized competing trials planned (no duplication of efforts).
- 3) There is a small window of opportunity to answer this question before whole blood becomes standard of care in the prehospital setting in many jurisdictions that would be difficult to reverse.
- 4) The UK is an optimal location to perform the trial with a publically funded healthcare system to support the costs of the blood products to be used in the trial (other countries would need 5x the funding to complete the same trial).
- 5) The applicants have stellar expertise in the conduct of clinical trials, including clinical trials in this challenging group of patient and I have confidence in their ability to complete the trial.
- 6) The applicants are nicely integrated into societies/healthcare organizations that will facilitate the knowledge translation at the end of the study period.
- 7) Trauma research is globally underfunded despite 24% of years of life lost being secondary to trauma (equivalent to cancer related years of life lost) – trauma research receives a fraction of the funding of cancer and other diseases despite its incredible impact on shortening the lives of young people.
- 8) They have proactively engaged a patient group to ensure outcomes are relevant to patients.

Weaknesses/recommendations for improvement:

- 1) The authors do not disclose strategies to mitigate the risks to patients transfused whole blood:
 - (a) will the whole blood be leukoreduced and be procured from only male donors (TRALI risk);
 - (b) potential risk from fresh viable lymphocytes (transfusion-related graft-vs-host disease: Gilstad C, et al. Fatal transfusion-associated graft-versus-host disease with concomitant immune hemolysis in a group A combat trauma patient resuscitated with group O fresh whole blood. *Transfusion*. 2012;52(5):930-5);
 - (c) Risk (and monitoring) of hemolysis in non-O recipients;
- 2) Mitigation strategies to reduce impact of the study on the NHSBT blood supply: (a) some countries have dedicated group O whole blood collection programs to mitigate effects on regular collections; (b) at 14 days converting the products to RBCs; (c) collection of data on wasted group O WB units (will the study be terminated at the internal pilot phase if the wastage rate is unacceptable?)
- 3) Pre-hospital death: randomized patients with pre-hospital cardiac arrests will be excluded, although it is unclear if this means patients who arrest and then are successfully resuscitated vs. pre-hospital deaths for randomized patients; patients will be identified by arrival logs (will this include deceased patients so no patients are lost to follow-up); the whole point of whole blood is to prevent pre-hospital cardiac arrests and deaths so critical that these patients are maintained in the ITT population; the statistical adjustment for excluding pre-hospital cardiac arrest on the randomized population is not stated (ie. The ITT population will not be as randomized); unclear how large the “arrest population” that will be excluded.
- 4) “WB enables faster administration of balanced resuscitation”: since the PROPPR trial was a negative trial it is unclear what the justification for achieving “balanced resuscitation”;
- 5) Pre-hospital TXA: since TXA under 1 hour of injury is critical to patient outcomes, what strategies will be undertaken to ensure 100% of patients in both arms receive this “standard of care” and that there is balance between the two groups;
- 6) Justification for the absolute difference in mortality: the systematic review failed to show any difference in mortality with whole blood vs. component therapy so it very unlikely that a 12% absolute difference will be found (Malkin M, et al. Effectiveness and safety of whole blood compared to balanced blood components in resuscitation of hemorrhaging trauma patients - A systematic review. *Injury*. 2021;52(2):182-188); after the internal pilot what will there be the stopping criteria for sample size recalculation for a much lower than anticipated effect size?; what will be the funding/sample size mitigation strategies if a CRASH-2 type numbers (n=20,000) are needed to look for a <1-3% difference; The authors cite a 13% absolute difference in mortality based on reference 19 (Williams et al 2019) but this paper cites this statement: With respect to 30-day survival, there was no difference between LTO-WB and COMP groups based on univariate analysis (73% vs. 74%, $p = 0.805$); They also cite two other papers (a) PAMPER – this study was plasma vs. nothing so cannot be used as this grant uses an active comparison; (b) PROPPR PLT study – this is comparing platelets in box 1 vs. box 2 and does not appear to be relevant;
- 7) Outcomes recommended by the NHLBI/NIH consensus conference on outcomes not used as recommended (6 and 24 hour total number of allogeneic blood products transfused); the consensus conference recommended against mortality as a primary outcome (itself a composite endpoint) due to the impact of TBI related deaths biasing the study towards the null hypothesis;
- 8) Age limits: the protocol has no age limit but no dose reduction provided for small children (ie. mL/kg equivalent to max 2 units of WB) or for that matter small women;
- 9) Life-threatening haemorrhage: this term is not defined and there does not appear to be standard activation criteria for use of pre-hospital blood;

- 10) Transfusion protocol throughout resuscitation: the NHLBI/NIH consensus conference strongly recommended that every haemostatic resuscitation trial should have a standard algorithm for all transfusions across all sites (not being standardized in this study);
- 11) Blinding: since this intervention happens in the pre-hospital setting every effort should be made to blind healthcare workers, outcome assessors, and patients/families to treatment assignment – suggest add strategies to minimize treatment allocation bias post hospital arrival (e.g., remove all completed units after infusion from iv tubing; all documentation should be generic “1 dose of “Study X” product administered”)
- 12) Notification of randomized patients by AA personnel: it appears as though the RNs will be tracking arrival of patient for randomized patients; since every case of product needs to be accounted for during the study, on return of every study product empty cooler there needs to be the name/number of the patient provided to the research team; other pre-hospital TXA/transfusion studies have also used a brightly coloured armband to alert receiving team that the patient is in the trial;
- 13) Internal pilot stopping criteria appear very lenient: The stopping criteria relate to enrolment rates (this is fine) and primary outcome completion <50% (since the primary outcome is death within 30 days 50% lost to follow-up would be very bizarre); I think stopping criteria based on sample size re-estimation based on overall mortality rate of 40% and effect size are probably more relevant to understanding at the end of the internal pilot if the trial as planned at 844 is likely to answer questions about the effectiveness and safety of WB;
- 14) Cost-effectiveness analysis: data for this will be collected manually by the research personnel – one would think that it would be more accurate and reliable to collect actual case-costing data from the NHS data;
- 15) Subgroup analyses (a priori): Suggest pre-specified subgroup analysis to include sex (women have differing outcomes after trauma and maybe more prone to volume overload from transfusion due to smaller blood volume).

The proposals competitiveness relative to the current state-of-the-art in the field

- **Feasibility:**

Proposed time frame appears realistic. Potential improvements are listed above and include: (a) standardized activation criteria for pre-hospital transfusion and define “life-threatening bleeding” to avoid inclusion of patients with low chances of death biasing results towards the null hypothesis; (b) perform an external multicentre pilot to provide some clarity on feasibility and justification for the effect size; (c) standardized transfusion protocol during first 24 hours of care; (d) strategies to reduce wastage of group O WB; (e) do not exclude pre-hospital deaths (the whole goal with pre-hospital WB is to save these patients); (f) improve blinding efforts throughout study (outcome assessors, healthcare personnel post trauma bay).

- **The likelihood of translating into clinical practice:**

There is no question that pre-hospital component therapy is more complicated for the bedside team to administer. If the speed with WB led to improved outcomes, the wastage of WB in the trial could be mitigated, and the cost of WB was cost-effective, there is likely to be uptake into clinical practice worldwide. The trial is likely to be negative and this would be very helpful for shutting down WB programs. WB programs are logistically difficult to run and have high wastage rates.

- **Whether the resources requested are appropriate:**

Cost for completion of the trial seems reasonable, perhaps on the lower end of the expected cost range for such a large complicated trial where many patients are in hospital for prolonged periods, the data collection is more complex, and the logistics of managing the WB supply are expensive.

Strength of the research team

Based on track record in relevant areas, how qualified are the applicants to undertake the work using the methodologies proposed? To what extent does the research team have the necessary breadth and depth of expertise to deliver the proposed work?

This is a very productive team with extensive experience performing clinical trials, including haemostatic trials. The team includes transfusion medicine, trauma/emergency, blood supplier, critical care, pre-hospital medicine, anesthesiology, biostatistics/methodology, and health economist. This is the strongest part of the grant.

Involvement of patients and the public:

Is there any patient and public involvement in the application, and if yes, is this appropriate?

Patient and public group has been established to oversee the design of the trial and its execution from the patient perspective.

Scoring

Rating of Application

The rating system has been designed to allow flexibility in assessing the strengths and weaknesses of an application within each category, as well as its quality overall.

- 10 Innovative outstanding work
- 9 Internationally competitive work at the forefront of its field
- 7 & 8 Internationally competitive work at the forefront of UK service enhancement/community engagement in this particular discipline
- 5 & 6 Nationally competitive work
- 3 & 4 Satisfactory work but not competitive
- 1 & 2 Unsatisfactory work that is seriously flawed in design

Scientific quality	8
Originality of the proposal	9
Importance of the area of research	9
Relevance of the work for clinical practice	9
Overall Rating	9

Reviewer Information

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Institute:	Queen's University, University of Toronto, Kingston Health Sciences Centre

Conflicts of Interest

Please declare any conflicts or potential conflicts of interest that you may have in undertaking this research:

Research outside of the UK on trauma but no overlap with whole blood. I was on the DSMB for only WB RCT trial published to date but this was 7-8 years ago (Cotton BA, Podbielski J, Camp E, et al. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg 2013; 258(4): 527-32; discussion 32-3).

Peer Review Form

Blood and Transplant

Research Code:	20/140
CI Name:	Dr Laura Green and Professor Jason Smith
Title of project proposal:	A randomised controlled trial of pre-hospital whole blood transfusion versus standard care for the resuscitation of patients with life-threatening haemorrhage.

Review

Please give an assessment of the strengths and weaknesses of the proposal, including your opinion regarding:

The current state-of-the-art in the field:

The current state of the art will depend on the results of ongoing trials (which will finish before the proposed start date within the application so no recruitment conflict). A substantial proportion of prehospital medical systems have moved to giving prehospital blood based on current evidence (and are not participating in the current trials due to lack of equipoise). It is therefore likely that blood and blood components will be the standard of prehospital care at the time of the proposed trial (which is as per the applicant's description of the control group in the proposal).

The proposals competitiveness relative to the current state-of-the-art in the field

- **Feasibility:**

The current prehospital blood and component trials have overcome many of the barriers, so following a similar method (as proposed in this application) makes the delivery of the project feasible. The recruitment rate in the proposed study will probably be higher than the known rate of recruitment in RePHILL, as the prehospital systems who do not have equipoise for a blood v crystalloid study will probably be able to recruit to a stored blood v whole blood study.

I think that the proposed study is probably under-powered. The assumption is that whole blood v stored blood in the prehospital phase (to a maximum of 2 units) will prevent a third of deaths in this complex and severely injured group. The studies used to determine the 12% absolute (30% relative) decrease in death are not really comparable – the PAMPER study used crystalloid resuscitation as a control and the PROPPR sub-study failed to account for the fact that all of the early deaths fell into the 'no platelets' group (as they did not live long enough to receive the second treatment box). Even with the high overall cost of the logistics of getting whole blood into the pre-hospital phase of care, the minimum clinically significant difference is much less than 12%, so I would recommend that the sample size calculation is revisited (especially in the light of the current low cost of the proposal).

However, it is also possible to argue that the sample size in the application is based on the best of the current evidence and so my 'non-evidence based' view that the proposal is under-powered should be ignored!

It is likely that the applicants will deliver the study within the time-line proposed.

- Are the proposed methods adequate • Is the proposed time for completion of the project realistic? • Could any improvements be made to the proposal?

- **The likelihood of translating into clinical practice:**

It is likely that if performed with the proposed sample size the study will (like many of the recent trauma intervention studies) find an effect that is greater than the minimum clinically significant difference, but smaller than the effect assumed in the sample size calculation (and hence will conclude 'no statistically significant difference'). This will not necessarily preclude adoption into UK practice as the trauma care community here is beginning to look at the 'best estimate of effect' of an intervention rather than just the p value, however this is not a universal view.

- **Whether the resources requested are appropriate:**

The overall budget (at £831,915 for a complex 36 month study) seems low for the scale of the study – however I can only see total cost in the application, so cannot make detailed comment.

Strength of the research team

Based on track record in relevant areas, how qualified are the applicants to undertake the work using the methodologies proposed? To what extent does the research team have the necessary breadth and depth of expertise to deliver the proposed work?

This is an internationally strong research team who have an excellent track record of successful delivery of interventional trials in trauma coagulation and prehospital care.

Involvement of patients and the public:

Is there any patient and public involvement in the application, and if yes, is this appropriate?

An appropriate PPI process in the development of the is described and there is an appropriate PPI plan for the project.

Scoring

Rating of Application

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- 5 & 6 Nationally competitive work
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- 1 & 2 Unsatisfactory work that is seriously flawed in design

Scientific quality	9
Originality of the proposal	9
Importance of the area of research	10
Relevance of the work for clinical practice	10
Overall Rating	9

Reviewer Information

Name:	Prof Tim Coats
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Conflicts of Interest

Please declare any conflicts or potential conflicts of interest that you may have in undertaking this research:

I have no conflicts of interest.

Research Code:	20/140
CI Name:	Dr. Laura Green and Professor Jason Smith
Title of project proposal:	A randomized trial of pre-hospital whole blood transfusion versus standard care for the resuscitation of patients with life-threatening haemorrhage

Review

Please give an assessment of the strengths and weaknesses of the proposal, including your opinion regarding:

The current state-of-the-art in the field:

The state-of-the-art in pre-hospital haemorrhage resuscitation is transfusion of blood products rather than crystalloid or colloid. The investigators provide a generally accurate overview of current resuscitation practices and their evolution but they omit details that are relevant to the conduct of the proposed trial. They note that the UK regulatory authority has approved whole blood for up to 14 days of storage. This short shelf life (compared to red cell concentrates and plasma) will restrict product availability. In the US and other jurisdictions, whole blood can be stored for 21 days in CPD anticoagulant and 35 days in CPDA-1. Studies of whole blood hemostatic potential suggest that changes in performance are minimal between days 14-35, regardless of anticoagulant (Pidcock et al. Transfusion 2013; Meledeo et al. Transfusion 2019) and that whole maintains hemostatic potential likely greater than what is available from red cell concentrates combined with plasma throughout shelf life. Furthermore, the authors propose to use Group O, low anti-A/low anti-B, Rh-negative whole blood as the test product compared to red cell concentrates and plasma. The requirement of using only Rh-negative products will severely restrict product availability. While prevention of alloimmunization in transfusion recipients is attractive, prevention of haemorrhage mortality is the greater priority. Most trauma systems around the world that have adopted whole blood have used O-positive as the main product due to availability and results appear to be comparable to component therapy (Sehault et al. Transfusion 2018; Yazer et al. Transfusion 2021). The combined effects of restricting shelf life to 14 days and use of only Rh-negative products will hamper trial logistics. In addition, these constraints will limit the generalizability of the study findings, since few blood systems will be able to support use of a 14-day/Rh-negative product when about 7% of the population is O-negative. It may be that the decision to pursue this testing strategy was informed by regulatory requirements, but the trial would be of greater international value if the investigators worked with regulators to craft an adaptive design that could explore the effects of extending shelf life and using O-positive blood. In summary, I think this trial will be extremely difficult to execute and will not provide generalizable data.

The proposals competitiveness relative to the current state-of-the-art in the field

- **Feasibility:**

As noted above, I am concerned about feasibility based on the decision to use only O-negative whole blood with a 14-day shelf life. I would further note that the trial summary provided did not include other important details regarding the test product:

- Since whole blood contains plasma, will only male donors be used, or will the study include female donors screened for anti-HLA antibodies as a TRALI mitigation measure? A male-only donor policy would further restrict product availability.
- What leukoreduction filter will be used? Has the effect of the filter on platelet function been assessed?
- Has modelling of out-date rates been performed? A 14-day shelf life for whole blood suggests the potential for significant product out-date and wastage, increasing costs.

Regarding trial design, I am concerned that comparing the administration of 2 units of whole blood pre-hospital to 2 units each of red cell concentrates and plasma, followed by component therapy for both arms is unlikely to demonstrate a difference in 30-day mortality (primary endpoint). The vast majority of patients needing pre-hospital transfusion and surviving to hospital admission will require substantial volumes of blood product resuscitation. The effects of 2 units of whole blood in perhaps 15-25 total blood products administered over the hospital course are unlikely to be detectable. The authors power their study based on several previous trials that are not really comparable. In PAMPer, 2 units of plasma were compared to “standard of care” – typically crystalloid or red cells and crystalloid. It is likely that whole blood would fare well in such a comparison, but against red cell concentrates with plasma, the added effects of the platelets and less dilute nature of whole blood may require greater patient numbers to detect an effect. Similarly, in PROPPR, early apheresis platelets (containing vastly more platelets than what is available in 2 units of whole blood) reduced mortality in the 1:1:1 arm compared to the 1:1:2 arm. However; the overall study failed to detect a clinically significant difference in 30-day mortality between the two arms. Therefore, I am concerned that the study proposed here will be terminated for futility at interim analysis. Tempering this concern is the possibility that patients in the plasma/RBC arm will not receive the full intervention due to the difficulty in administering four products through limited IV access in the pre-hospital environment. Information regarding the success rate in administering the full 2+2 protocol could be obtained from a retrospective review of air ambulance operations or a pilot phase to this study and might be helpful in resolving these questions.

A direct comparison of whole blood vs. components – carried through the entire patient resuscitation or at least most of it (say, first 6 hours) – would answer the question as to which strategy is superior. As is, this study will almost certainly be negative, if indeed it can be executed given the logistical challenges highlighted above.

• *Are the proposed methods adequate* • *Is the proposed time for completion of the project realistic?* • *Could any improvements be made to the proposal?*

- **The likelihood of translating into clinical practice:**

As discussed above, I don't think this trial is really feasible and is probably futile given the dilution of any whole blood effect in the overall resuscitation based on component therapy, particularly if the primary endpoint is 30-day survival.

In addition, see comments above regarding 14-day shelf life and use of exclusively O-negative whole blood – no other trauma system is going to use O-negative, 14-day whole blood.

- **Whether the resources requested are appropriate:**

The main resource problem is the whole blood product as conceived.

Strength of the research team

Based on track record in relevant areas, how qualified are the applicants to undertake the work using the methodologies proposed? To what extent does the research team have the necessary breadth and depth of expertise to deliver the proposed work?

The team is very strong and has several internationally known experts in trauma and transfusion medicine.

Involvement of patients and the public:

Is there any patient and public involvement in the application, and if yes, is this appropriate?

This appears to be adequately addressed.

Scoring

Rating of Application

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Scientific quality	2
Originality of the proposal	4
Importance of the area of research	9
Relevance of the work for clinical practice	4
Overall Rating	2

Reviewer Information

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Conflicts of Interest

Please declare any conflicts or potential conflicts of interest that you may have in undertaking this research:

None. I am active duty officer in the U.S. Army. The views expressed above are mine exclusively and do not reflect the official position of the U.S. Army or the U.S. Department of Defense.