JRMO Research Protocol for Research Studies

Full Title **An *evaluation* of leucocyte depleted red cells and plasma transfusion for major traumatic haemorrhage in patients presenting to the pre-hospital setting in London – feasibility study**

Short Title Red blood cells and plasma transfusion in the pre-hospital setting.

Sponsor Queen Mary University of London

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List of technical departments *Not applicable*

List of central facilities *Not applicable*

1. Contents

2. Glossary

CI	Chief Investigator
CRF	Case Report Form
FFP	Fresh frozen plasma
JRMO	Joint Research Management Office
NHSBT	NHS Blood and Transplant
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
RBC	Red blood cells
RC&Plasma	Red cells and plasma
RLH	Royal London Hospital

3. Signature page

Chief Investigator Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

Chief Investigator Name: **Dr Laura Green**

Signature: 

Date: **11.04.2018**

4. Summary and synopsis

Short title	Red blood cell and plasma transfusion in the pre-hospital setting
Methodology	Observational Cohort study collecting anonymised data only
Objectives / aims	***Primary objective*** Assess the feasibility of delivering RC&Plasma components into clinical practice. ***Secondary objectives*** Compare the impact of RC&Plasma transfusion with red blood cell (RBC) transfusion (retrospective data) and RBC and fresh frozen plasma (FFP) transfusion (prospective data from Newcastle and Oxford hospital) on: resuscitative effect (base excess, lactate), coagulation parameters, overall transfusion requirement, haemolysis, days in hospital and mortality, in trauma bleeding patients.
Number of participants	*140 in the RC&Plasma arm* *200 in the RBC arm (retrospective)* *150 in the RBC and FFP arm*
Inclusion and exclusion criteria	Inclusion criteria - All trauma patients requiring pre-hospital major haemorrhage protocol activation by the pre-hospital team because of haemorrhagic shock and for whom clinician has transfused a RC&Plasma component (in London), or RBC and FFP by either the Great North or Thames Valley Air Ambulance. - Patients who have received at least one RBC unit in the pre-hospital setting because of trauma haemorrhage between March 2015 and April 2018 (retrospective cases) -
Study duration	*2 years*

5. Introduction

Uncontrolled bleeding due to trauma is associated with significant morbidity and mortality, and substantial costs to NHS. Early administration of fresh-frozen-plasma (FFP) and platelets in a high (near 1:1:1) ratio with red blood cells (RBC) reduces mortality, and this has now become standard of care for trauma patients who are bleeding. However, the logistics of delivering FFP together with RBC in the pre-hospital setting could delay transfer to hospitals (which could be detrimental), and also place additional demands on the clinical team. Availability of a component that contains red cells and plasma (RC&Plasma) in a single bag could overcome these challenges. Such component is available in the UK: however, it is not used routinely. Furthermore, the efficacy and safety relative to other transfusion strategies have not been investigated in randomised controlled trials.

The Royal London Hospital Major Trauma Service and the Helicopter Emergency Medical Service, have made a clinical decision to change standard treatment for the management of trauma patients who are bleeding in the pre-hospital setting, from the transfusion of RBC to the transfusion of RC&Plasma for 24 months.

The overall objectives of this project are to:

a. assess if it's feasible to deliver RC&Plasma component to patients who are bleeding in the pre-hospital setting, so that we can lay the groundwork for a future trial that will compare the efficacy and safety of different transfusion strategies
b. evaluate the impact of the RC&Plasma transfusion in trauma bleeding patients in the pre-hospital setting on: transfusion requirements, rate of haemolysis, resuscitative effect, days in hospital, rate of thrombosis, and mortality by comparing these with RBC transfusion only (using retrospective data) and RBC and FFP transfusion (prospective data from Newcastle and Oxford hospitals);

5.1. Background

5.1.1. Transfusion management of trauma bleeding

Uncontrolled bleeding accounts for 40% of all trauma deaths with the costs of management being around £150 million for the NHS (Campbell, *et al* 2015). A timely and organised approach to transfusion in the management of bleeding is crucial to improving clinical outcomes. In 2015, a randomised controlled study (PROPPR) showed that early administration of fresh frozen plasma (FFP) and platelets in a 1:1:1 ratio with red blood cells (RBC) reduces death from exsanguination at 24 hours compared with a 1:1:2 ratio (Holcomb, *et al* 2015), and these results informed national guidelines on the management of major bleeding recommending that FFP be given empirically and early in the initial resuscitation process in 1:1 ratio with RBC ([NG39] 2016, Hunt, *et al* 2015). The precise role of platelets is unclear, with recent guidelines being unable to make any strong recommendations for platelet transfusions. There is some evidence that platelet transfusions may be more effective when given very early in the clinical course of bleeding (Holcomb, *et al* 2015).

In March 2012 for the first time in the UK, the Royal London Hospital allowed the pre-hospital team to transfuse RBC on-scene to trauma patients who were bleeding: this has contributed to reduction in the pre-hospital mortality from 42% in 2009 to 27% in 2015 ($p < 0.01$). However, in the pre-hospital setting the logistics of delivering FFP in addition to RBC could be quite challenging as this would: a) necessitate additional weight for the pre-hospital personnel approaching the scene of the accident; b) increase the complexity of resuscitating patients because several bags (blood and fluid) would need to be administered to a patient who may not have enough intravenous access, and clinical team are occupied doing other important tasks; and b) delay the transfer of patients to hospital because clinical team would attempt to transfuse both RBC and FFP at the scene, which could be potentially detrimental to outcome (Meyer*, et al* 2017). While some trauma centres like Newcastle and Oxford have decided to transfuse RBC and FFP in the pre-hospital setting, clinicians realise that a single whole blood (WB) product that contains everything in one bag (RBC, FFP and Platelets) would be ideal, but this is not yet possible in the UK due to current manufacturing procedures removing platelets from WB donations. Another product that contains RBC and FFP in one bag (RC&Plasma thereafter) is available in the UK, and has been used in the past, but it is not currently in routine use. Moreover, studies comparing its efficacy and safety, against standard blood components have not been conducted.

5.1.2. Blood components

Whole blood component (WB) was used routinely by the military between 1940 to 1960 to treat soldiers during World War II, Korean War, Vietnam War, and also in the most recent conflicts in Bosnia, Kosovo, and Iraq. This component was transfused to patients within 24 hours of it being donated (known as fresh WB). By 1965 the use of fresh WB reduced significantly due to the introduction of blood components (i.e. RBC, FFP, Platelet), which made targeted replacement therapy of missing clotting factors possible, and in so doing it minimized the potential risks and side effects of receiving unneeded blood components. Further, the longer shelf-lives of blood components, compared with fresh WB, made the logistics of supply and demand more manageable for the blood manufacturing units. All these contributed to the rapid disappearance of (fresh) WB.

In the UK all blood components have to undergo removal of leucocytes (called leucocyte - depletion) as a safety measure to reduce the risk of variant-CJD transmission. However, the filters that are used will also remove platelets in addition to leukocytes, thus the remaining component will contain only red cell and plasma (or RC&Plasma thereafter). Since the introduction of the leucocyte depletion process in 1999, NHSBT has issued approximately 3,000 units of RC&Plasma components. This component is not currently routinely issued to hospitals, albeit around 1,000 units per year of a similar product (containing a lower plasma volume of ~50mL) has been issued by NHSBT to support intrauterine and neonatal transfusion since 1999.

5.2. Rationale

In the recent years there has been a huge interest in revisiting the transfusion of RC&Plasma component in bleeding patients, particularly for those presenting with trauma in the pre-hospital setting, and where support with plasma transfusion in addition to red cells, could be quite challenging. However, studies evaluating its efficacy and safety against standard care are non-existent, and prior to performing such studies, we need to first establish the feasibility of making this component available to pre-hospital teams, considering that it has a shorter

shelf-life than RBC (14 versus 35 days), and that its production could increase hospital blood wastage, and also impact the manufacturing of other blood components needed for other settings.

A clinical decision has been made by the Royal London Hospital (RLH) Major Trauma Service and the Helicopter Emergency Medical Service, to change standard treatment for the management of trauma patients who are bleeding in the pre-hospital setting, from the transfusion of RBC to transfusion of RC&Plasma component, for a period of 2 years beginning June 2018. Some medical services like Great North Air Ambulance and Thames Valley Air Ambulance have decided to transfuse RBC and FFP in the pre-hospital setting.

The overall aim of this project is to assess if it's feasible to deliver RC&Plasma component (and eventually whole blood by extension) to patients who are bleeding in the pre-hospital setting, so as to lay the groundwork for a future trial that will compare the efficacy and safety of different transfusion strategies.

5.3. Risks / benefits

This is an observational study that will assess if it is operationally possible to deliver RC&Plasma component to patients who are bleeding in the pre-hospital setting, with the view to performing a future randomised control trial that will compare different transfusion strategies. RC&Plasma component has been used in the past in the UK without any safety concerns, and from June 2018 the RLH Major Trauma Service and the Helicopter Emergency Medical Service have made a clinical decision to transfuse this component (instead of RBC) to trauma patients who are bleeding in the pre-hospital setting. The main benefit of the study will be to inform the future trial, which in turn will improve transfusion treatment of bleeding patients.

6. Study objectives

6.1. Primary objective

- Assess the feasibility of delivering RC&Plasma component into clinical practice and understand the operational and financial impact (for both NHSBT and NHS hospitals) of implementing the RC&Plasma component into clinical practice in the future.

- Determine RC&Plasma wastage in hospital

6.2. Secondary objective

Compare the impact of RC&Plasma transfusion with RBC transfusion (retrospective data between March 2015 to April 2018) and RBC and FFP transfusion (prospective data from Newcastle and Oxford hospital) on: resuscitative effect (base excess, lactate), coagulation parameters, overall transfusion requirement, haemolysis, days in hospital and mortality, in trauma bleeding patients.

6.3. Primary endpoint

1. Percentage of 'On-time-in-Full' (OTIF) delivery from NHSBT to RLH, defined as:
- occasions when product is delivered to agreed / requested schedule, and
- occasions when product delivered to specification,

Therefore, OTIF will be Percentage of occasions per annum where component was delivered as specified and as scheduled or requested.

2. Wastage of RC&Plasma component at Royal London Hospital per anum.

Data on both outcomes will be collected monthly and aggregated at study end.

The results of this study will be used to build a model that can predict wastage using user-specific parameters such as: demand for RC&Plasma in pre-hospital and hospital trauma settings and day-to-day deliverability of RC&Plasma, with a view to determining the optimum pattern of supply that will adequately meet demand and yet result in minimal wastage for individual hospitals.

6.4. Secondary endpoint

To evaluate the clinical impact of RC&Plasma transfusion versus RBC transfusion and RBC and FFP transfusion, the following clinical data will be collected:

- Changes in base deficit and prothrombin time from scene to emergency department
- Transfusion wastage (red blood cells, fresh frozen plasma, platelets, cryoprecipitate) at 24-hours post injury
- Transfusion requirement at 24 hours and up to hospital discharge or 28 days, or death – whichever occur first
- Total hospital length of stay
- Survival analysis up to 24-hours and 28 days post injury

Other factors that will be monitored include:

NHSBT

- Wastage (units per month)
- Substitutions (units per month)
- Impact on supply of other blood components
- Impact on other processes
- Additional administration resources and time required to provide RC&Plasma

Hospital

- Additional administration support and time required to support clinical team
- % of RC&Plasma used in the pre-hospital setting
- % of RC&Plasma used in emergency department

7. Study population

7.1. Inclusion criteria

RC&Plasma cohort

- All trauma patients >1yr old requiring prehospital major haemorrhage protocol activation by pre-hospital team in London, or trauma team lead at the Royal London hospital.
- Haemorrhagic shock
- Patients who have started or have received at least one RC&Plasma unit in the pre-hospital setting because of haemorrhage

Comparator groups

RBC cohort (retrospective data)
All trauma patients who have been transfused RBC in the pre-hospital setting in London (and emergency department at RLH) from March 2015 to April 2018.

RBC and FFP cohort (prospective data)
All trauma patients who have started or have received at least one RBC and FFP unit in the pre-hospital setting because of haemorrhage at Newcastle and Oxford hospitals

7.2. Exclusion criteria

None

8. Study design

Feasibility, observational cohort study.

RC&Plasma transfusion will replace RBC transfusion in the pre-hospital setting in London, and will be available for transfusion in hospital at RLH for trauma patients >1yrs old. Operational and clinical data relating to administration of RC&Plasma component will be compared with historical data of RBC transfusion in the pre-hospital setting in London from March 2015 to April 2018.

Newcastle and Oxford hospitals will continue to administer RBC and FFP transfusion in the pre-hospital setting.

9. Study procedures

9.1. Case Identification

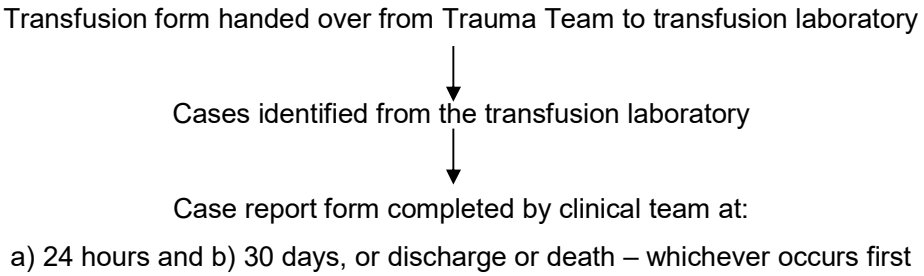
In the UK, it is a legal requirement that all hospital blood transfusion laboratories have a system in place to document the final destination of every blood component issued, so that any probable recipient-related transfusion complications (e.g. infections) can be traced back to donors, so that appropriate measures can be taken (BSQR 2005). These records must be kept in the transfusion laboratories for 30 years.

Therefore, all cases will be identified from the transfusion laboratories at three sites - the RoyaL London Hospital (RLH), John Radcliffe Hospital, Oxford and Royal Victoria Infirmary,

Newcastle Hospital. The RLH supplies blood to pre-hospital team for whole of London, and therefore RLH laboratory will keep records of all units issued and transfused (see diagram below).

Transfusion laboratories will only inform the central team at Barts Health of the date/time when blood was transfused in the pre-hospital setting, the name of hospital that the patient was admitted to, and the unique donation number of the transfused units. No patient' identifiers will be given to the central team. Once the central team has been informed of the case, the clinical team on the relevant site will be contacted and asked to submit the case report form (CRF) for the identified case using patient's case notes.

Study Scheme Diagram



9.2. Data collection

Operational data
Operational data regarding the deliverability and supply of blood will be collected on monthly basis from NHSBT and transfusion laboratory.

Clinical data (prospective)
Data will be collected from the clinical team at six sites. Once a case has been identified, the clinical team on each site will be asked to complete the CRF for case using a unique identification number – this will be a sequential number for each site. The completed CRF will be emailed to the central team at Barts Health Trust using nhs.net email accounts.

Study cases will not be contacted or approached for consent and NO identifiers (i.e. names, addresses, dates of birth, hospital or NHS numbers, or date of death) will be sought in the CRF. Respondents will be asked to keep their own record of the unique study number and the patient identifiers in order to facilitate elimination of duplicate reports or raise further queries if required.

The CRF will be made up of two parts and will seek information as described in Table 1.

Table 1. Variables that will be collected on the Case Report Form

Part 1: At presentation and within 24 hrs of blood transfusion in pre-hospital setting (or emergency department for RLH)
- Gender and age - Co-morbidities

- Date of transfusion for RC&Plasma (and RBC and FFP)
- Number of units transfused (or ml/Kg for children)
- Donation number for each RC&Plasma transfused
- Amount of crystalloid/colloid administered in 24 hours
- Severity of injury
- Laboratory results (Haemoglobin, platelet, coagulation tests, lactate results) from scene to ED and within 24 hours
- Patient's blood group
- Blood transfusion requirements in the first 24 hours
- Time of death (in hours) from administration of RC&Plasma (or RBC only, or RBC and FFP), and cause of death
- Transfusion reactions

Part 2: At 30 days, or discharge, or death or transfer to another hospital, (whichever is first)

- Date of discharge
- Thrombotic event (arterial or venous)
- Blood transfusion requirements
- Transfusion reactions
- Number of ventilator free days
- Number of intensive care units-free days
- Hospital length of stay
- Time of death (in days) from administration of RC&Plasma (or RBC and FFP), and cause of death

Retrospective data
Similar information as described in Table 1 will also be collected for trauma patients who have received RBC transfusion in the pre-hospital setting in London between March 2015 to April 2018. Cases will be initially identified from transfusion laboratories at RLH, and once the case has been identified other sites will be asked to submit anonymised clinical information on identified cases using patient's clinical notes and patient's electronic data.

Each case will be given a unique identifier, and no patient's identifier will be collected on the CRF or transferred to the central team at Barts Health.

9.3. Facilitation of data returns

Every month the central team will send reminders to clinical teams on each site for any new cases that need reporting. Further, for cases where part one of the CRF has already been submitted, the central team will send reminders to sites after four weeks, and another reminder two weeks later. If there is still no response after a further three weeks, the clinician will be contacted by telephone.

9.4. Follow up

Until discharge, or death, or 30 days after whole blood transfusion - whichever occurs first.

9.5. End of study definition

Two years after starting the transfusion of RC&Plasma component at RLH.

10. Statistical considerations

10.1. Sample size

Primary Outcome:

The primary outcome is the percentage of occasions per annum where component was delivered as specified and as scheduled or requested from hospital. It has been agreed between RLH and NHSBT that RC&Plasma component will not be delivered during bank holidays, and in these days 'On-time-in-full' calculation will be excluded. The current NHSBT OTIF standard is 98%. The study will be declared feasible if OTIF is achieved in at least 97.3% (95%CI: 95.7% - 98.4%).

The criteria for progression on wastage level is given under section 13.3 below.

Secondary Outcomes:

Since March 2012 when the Royal London team started carrying RBC on board, on average 70 patients per year have been transfused an average of 2 units of RBC in the pre-hospital setting. We therefore project that around 140 patients will be transfused with a RC&Plasma component during the study period (24 months). Based on The London ambulance data analysis of patients, approximately 70% of trauma patients who receive a RBC transfusion arrive in emergency department with a Base Deficit >6 mEq/L. Assuming a retrospective cohort of approximately 160 patients and at least 60 patients in the RC&Plasma arm, the study will have 80% probability (power) at 5% level of significance of detecting an absolute 20% reduction in the proportion of patients arriving in emergency department with a Base Deficit >6 mEq/L in the RC&Plasma group. The required sample size is attainable even after postulating a loss-rate of 25% (e.g. blood samples not being taken due to patients dying etc.).

10.2. Method of analysis

Statistical analyses will be performed using STATA (StataCorp, USA). Categorical variables will be tabulated as frequencies and percentages and compared using Fisher's exact tests; continuous variables will be summarised as means [standard deviation] or medians [interquartile range] and compared using t-tests or non-parametric equivalents. All tests will be two-sided at the 5% level of significance. Multivariable regression models will be used to examine the association between treatment groups (RC&Plasma versus RBC-only transfusions) and various clinical outcomes, controlling for potential confounders (including but not limited to: type and location of injury; age; other co-morbidities) as appropriate.

10.3. Criteria for progression

Feasibility objectives and related data to be collected	***Go criteria to proceed to full trial (Eldridge, et al 2016)***	***Criteria to reassess and adjust full trial protocol (Eldridge, et al 2016)***	***Stop criteria (Eldridge, et al 2016)***	***Rationale***
Component Wastage				
i) Rate of component wastage	*≤8% wastage*	*9% - 30% wastage*	*>30% wastage*	*On average RBC wastage is 2.5%. With the shorter shelf life of RC/Plasma at 14 days it was decided that 8% wastage would be the acceptable limit* ***Monitored on a weekly basis.*** ***Reason for wastage will be documents***
Stock Management				
ii) Days without component in the lab (per year)	*0 -5 days*	*6 - 15 days*	*>15 days*	*Ideally for the study to work and to assess feasibility of using this component there should be 0 days with no component.* ***Monitored on an monthly basis.***
iv) Number of components being transferred to ED on day 10	*90% -100% of units*	*70-89% of units*	*<70% of units*	***Monitored on a weekly basis.***
Clinical Factors				
v) Number of components used inappropriately in ED to	*0% - 5% of units*	*5 -20% of units*	*>20% of units*	*In 2016 of the Incorrect blood components transfused 20% were*

Feasibility objectives and related data to be collected	***Go criteria to proceed to full trial (Eldridge, et al 2016)***	***Criteria to reassess and adjust full trial protocol (Eldridge, et al 2016)***	***Stop criteria (Eldridge, et al 2016)***	***Rationale***
non-trauma, non-bleeding patients				*the wrong component and of that 10% were given by the clinical team.*
vi) Number of components used inappropriately in ED to non-trauma, but bleeding patients	*≤ 10% of units.*	*10 -25% of units*	*>25% of units*	***Monitored on a weekly basis.***
vii) Number of patients who received >4 units of RBC/ Plasma component	*≤ 2% of patients*	*3 -10% of patients*	*>10% of patients*	***Monitored on a weekly basis.***

ED: emergency department

10.4. RC&Plasma metrics

NHSBT
Nr units produced (p.a)
Stock outage (p.a.)
Delivered on time (%)
Delivered in full (%)
Substitutions n / annum (%)
Ad hoc deliveries n / annum
Reduced operator hours (whole supply chain) n / annum
Additional operator hours expended n / annum
Administration costs £ / unit
Total cost of delivery £ / unit
Adverse impact on other processes
Beneficial impact on other processes
Adverse impact on other components
Beneficial impact on other components
Adverse impact on testing and QM
Bank holiday management issues
Wastage n /annum
RLH
Nr unit transfused (p.a.)
Nr unit transfused Pre-hospital
NR unit transfused ED (% / p.a.)
Nr unit wasted (% / p.a.)
Nr unit wasted lab (% / p.a.)
NR unit wasted clinical area (n / p.a.)
Inappropriate use (n / p.a.)
Impact on other component
Transport cost
Bank holiday management issues
Pre-hospital setting
Time on scene

11. Ethics

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki the Principles of Good Clinical Practice (GCP), European

Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the UK Policy Framework for Health and Social Care Research (V 3.3, 07/11/2017) and any other applicable national regulations.

The primary ethical and management issues surrounding the proposed study are adequate data protection. In order to address this, we will only collect anomymised data and, the investigators will allocate each case a unique reference number. This number will be shared with the clinical team at other sites and will be used for all subsequent data collection, storage, and transfer.

The primary study database (MS Access) will be stored on a password−protected computer at Barts Health NHS Trust (in the office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital) and will be analysed by the study statistician at Queen Mary University of London: these locations are restricted to Trust haematology staff and academic staff respectively. The study database will be encrypted using the Windows XP Encrypting File System (EFS). Separate back−ups of the study database and the reference number key will be performed weekly using two storage drives stored in secure, fire−proof locations within the building.

The data will be accessible only by the key members of the working group, who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after a successful application to a Research Ethics Committee.

11.1. Annual Safety Reporting

Not applicable, as the study is only collecting anonymised data on patients who are treated as part of routine standard care. As such, standard procedures in relation to reporting and management of adverse events will apply, and this include reporting of transfusion related adverse events to Serious Hazzard of Transfusion and Serious Adverse Blood reactions and Events, as required under the regulations of the EU Blood Directive.

12. Public involvement

Patient and Public involvement (PPI) will play an important part on how the study findings are disseminated to public and local community, and how the definitive trial is designed and performed. We will work with members of trauma PPI group (Patient Advisory for Injury Research, at Trauma Science Institute), which has a lot of experience with transfusion related studies in trauma and is currently supporting a UK multicentre randomised control trials of cryoprecipitate transfusion in trauma (CRYOSTAT-2 trial, NIHR funded) that KB (chief investigator) and LG (co-investigator) are running.

We will also engage with the National Blood Transfusion Committee, that meets bi-annually. The committee brings together a diverse membership of clinicians in the

UK, and its input is crucial to steering and finalising the future strategy of transfusion management in bleeding patients, in trauma and other disciplines. We will also work with London Air Ambulance to engage with members/clinicians in the pre-hospital setting in the UK.

13. Data handling and record keeping

13.1. Data management

The team will consist of study co-investigators and statistician. Study investigators will have access to the central database, which will not contain any patient identifiers. The chief investigator will ultimately oversee and ensure study adherence with appropriate NHS guidelines.

Upon online receipt of the anonymised information of data collection forms via a Secure Sockets Layer (SSL) 128−bit encrypted, password−protected server, the investigators will allocate each participant a unique reference number. This number will be shared with the clinical team at other sites and will be used for all subsequent data collection, storage, and transfer.

The primary study database (MS Access) will be stored on a password−protected computer at Barts Health NHS Trust (in the office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital) and will be analysed by the study statistician at Queen Mary University of London: these locations are restricted to Trust haematology staff and academic staff respectively. The study database will be encrypted using the Windows XP Encrypting File System (EFS). Separate back−ups of the study database and the reference number key will be performed weekly using two storage drives stored in secure, fire−proof locations within the building.

The data will be accessible only by the key members of the working group, who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after a successful application to a Research Ethics Committee.

13.2. Source Data

Data will be collected from the clinical team at six sites using patient's clinical notes and electronic patient records. Once a case has been identified, the clinical team on each site will be asked to complete the CRF for case using a unique identification number – this will be a sequential number for each site. The completed CRF will be emailed to the central team at Barts Health Trust using nhs.net email accounts.

Study cases will not be contacted or approached for consent and NO identifiers (i.e. names, addresses, dates of birth, hospital or NHS numbers, or date of death) will be sought in the CRF. Respondents will be asked to keep their own record of the unique study number and the patient identifiers in order to facilitate elimination of duplicate reports or raise further queries if required.

13.3. Confidentiality

13.3.1. Participant confidentiality

In order to maintain patient confidentiality, no identifiable information will be collected as outlined above. The clinical team will not seek to collect any names, dates of birth, addresses, hospital or NHS numbers in order that none of the participants are individually identifiable.

13.4. Record retention and archiving

The research data will be archived for 20 years according to Queen Mary University of London/ Barts Health NHS Trust policy. The data will be archived in the Modern Records Facility, 9 Prescot Street, Aldgate, London, E1 8PR

14. Safety reporting

Due to the nature and design of this study, safety reporting of adverse events will not occur. Patient will be monitored and treated as part of routine care, and hospital staff will be responsible for reporting all transfusion related adverse events to Serious Hazzard of Transfusion and Serious Adverse Blood reactions and Events according to standard procedures, as required under the regulations of the EU Blood Directive.

15. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable.

16. Study committees

This is an observational study that will collect anonymised data on patients who have been transfused blood for management of traumatic haemorrhage. As such, the study does not require any data monitoring/steering/safety committees set up

The study will be managed by the management group below, with the CI overseeing the whole study.

NHSBT

Dr Rebecca Cardigan	Director of Component Development Laboratory
Kirk Beard	Supply Chain Specialist
Jane Davies	Manufacturing Development
Dr Heidi Doughty	Component team
Dave Edmondson	Head of Manufacturing and Product
Antonia Hyde	Hospital Services
Al Hunter	Customer Services

Dena Ghatt	Continuous Improvement Team
Dr Laura Green	Component team (CI)

The Royal London Hospital

Professor Karim Brohi	Trauma Surgeon
Dr Ross Davenport	Trauma Surgeon
Dr Laura Green	Haematologists (CI)
Julia Lancut	Transfusion laboratory manager
Josephine McCullagh	Transfusion Practitioner
Dr Anne Weaver	Consultant for Emergency Medicine

The study management group will work closely with PIs, patient and public and other collaborators to ensure that the study meets its objectives.

17. Finance and funding

This study is funded jointly by Barts Charity and London Air Ambulance. A full time equivalent Band 6 researcher assistant will be employed for 2 years to co-ordinate the data collection and cover other administrative tasks

A band 7 scientist (0.4 whole time equivalent) will support the data collection for the transfusion laboratory at RLH – this post is funded by the haematology department at Barts Health Trust.

NHS Blood and Transplant has agreed to ensure a component price for the product to be used in the above study equivalent to a cost saving of £50 for every 'red cell and plasma' unit issued to the Royal London Hospital as part of the study. It is anticipated that around 1,500 units will be used during the study period, equating to an effective grant of £75,000.

18. Insurance and indemnity

It provides cover for the design, management, and conduct of the study.

The Joint Research Office has arranged for suitable indemnity concerning negligent harm to be in place for this study. The insurance that Queen Mary University of London has in place provides "No Fault Compensation" for participants which provides an indemnity to participants for non-negligent harm.

19. Dissemination of research findings

The data from this study will be analysed and the results published as soon as possible in a scientific journal after study completion. The information will be published and distributed to all participating clinicians, as well as being presented at scientific meetings.

20. References

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This protocol is based on JRMO Protocol template for Research Studies; version 1.0, February 2018.