NHS
Blood and Transplant

SWiFT

Study of Whole blood In Frontline Trauma

A Multi-Centre Randomised Controlled Trial of the Clinical and Cost Effectiveness of Pre-Hospital Whole Blood Administration versus Standard Care for Traumatic Haemorrhage.

TRIAL PROTOCOL
v1.1, dated 03/05/2022

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ClinicalTrials.gov: [TBC]
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REC: 22/SC/0072
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This protocol has regard for the HRA Guidance.

Protocol Signature Page

The undersigned confirms that the following protocol has been agreed and accepted and the Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Approved by:

Name	Role	Signature	Date
Laura Green	Chief Investigator	Approved electronically	04/05/2022
Jason Smith	Chief Investigator	Approved electronically	04/05/2022
Helen Thomas	Lead Statistician	Approved electronically	04/05/2022
Katie Keen	QA Representative	Approved electronically	04/05/2022
Oluwayomi Adegbaju	Sponsor Representative	Approved electronically by Alice Bell on behalf of Oluwayomi Adegbaju	06/05/2022

Key Trial Contacts

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Funders	• Air Ambulance Charities: [listed in Appendix 1] • NHS Blood and Transplant • Ministry of Defence
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i. Contents

ii. Abbreviations and Glossary

AAS	Air Ambulance Service
AE	Adverse event
AIS	Abbreviated Injury Score
AR	Adverse reaction
ATR	Acute Transfusion Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DH	Department of Health
DM	Data Manager
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ED	Emergency Department
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
HRA	Health Research Authority
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ISF	Investigator Site File (part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
ISS	Injury Severity Score
JPAC	Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MTC	Major Trauma Centre
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NHSBT	NHS Blood and Transplant
NHSBT PPAG	NHS Blood and Transplant Patient and Public Advisory Group
PALS	Patient Advice and Liaison Service
PCC	Prothrombin Complex Concentrate
pH	Potential of Hydrogen (measurement of acidity or basicity)
PI	Principal Investigator
QA	Quality Assurance
QoL	Quality of Life
R&D	Research and Development
RBC	Red Blood Cells
RCP	Red Cells and Plasma
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SABRE	Serious Adverse Blood Reactions and Events
SACBC	Standing Advisory Committee on Blood Components
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SHOT	Serious Hazards of Transfusion
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWiFT	Study of Whole blood in Frontline Trauma
TACO	Transfusion Associated Circulatory Overload
TAD	Transfusion Associated Dyspnoea
TARN	Trauma Audit and Research Network
TCA	Traumatic Cardiac Arrest
TRALI	Transfusion Associated Acute Lung Injury
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UAR	Unexpected Adverse Reaction
UTRE	Unexpected Transfusion Related Adverse Event
WB	Whole Blood

iii. Trial Synopsis

Title of Clinical Trial	A Multi-Centre Randomised Controlled Trial of the Clinical and Cost Effectiveness of Pre-Hospital Whole Blood Administration versus Standard Care for Traumatic Haemorrhage.	
Protocol Short Title	SWiFT: Study of Whole blood In Frontline Trauma	
Study Design	• Multi-centre, interventional, randomised, unblinded, parallel controlled trial • Phase III CTIMP • Participants will be randomised 1:1 to intervention and comparator • Within-trial cost-effectiveness analysis • Qualitative research to assess implementation of the intervention	
Trial Participants	Patients (adults and children) attended by participating Air Ambulance Services, who have suffered major traumatic haemorrhage.	
Planned Sample Size	848 participants	
Treatment duration	As required by the treating clinician until arrival at the Emergency Department.	
Follow-Up Duration	3 months	
Planned Trial Period	36 months (recruitment period: 24 months)	
Health Condition Studied	Major traumatic haemorrhage	
Setting	Pre-Hospital Emergency Medicine	
Interventions to be compared	**Intervention arm:** Up to two units of whole blood (WB). **Comparator arm:** Up to two units of red blood cells and two units of plasma (either thawed Fresh Frozen Plasma (FFP) or freeze-dried plasma (LyoPlas)).	
	Objectives	Outcome Measures
Primary	The primary objective is to determine whether pre-hospital leukocyte-depleted whole blood transfusion is better than standard care (component transfusion) in reducing the proportion of participants who experience death or massive transfusion at 24 hours.	Proportion of participants who have died (all-cause mortality) or received a total of 10 or more units of any blood components in the first 24 hours from randomisation (a participant is considered randomised and entered into the trial when the trial intervention box has been opened).

Secondary	Secondary objectives will compare: - Mortality up to 90 days - Morbidity up to 30 days - Hospital resource use up to discharge, including organ failure free days, time spent in critical care and total in-patient stay, blood components and additional haemostatic agents received - The cost-effectiveness of pre-hospital whole blood administration versus standard care for traumatic haemorrhage. - Health-related quality of life at 90 days - Safety	• Proportion of participants who received a total of 10 or more units of any blood components in the first 24 hours from randomisation • All-cause mortality at 6 hours, 24-hours, 30 days and 90 days from randomisation. • Number of organ failure free days up to 30 days, defined as the number of days free of advanced cardiovascular, advanced respiratory and advanced renal support • Days in critical care and separately in an acute care hospital (up to 90 days). • Units of each blood component received in the 24 hours after randomisation (including prehospital transfusions): WB, RBC, plasma, platelets and cryoprecipitate. • Amount of cell salvage received at 24 hours (in mLs) after randomisation • Number of participants receiving additional haemostatic agents received at 24 hours after randomisation: recombinant Factor VIIa, fibrinogen concentrate, prothrombin complex concentrate (PCC), tranexamic acid (TXA). • Presence of coagulopathy (defined as prothrombin time above the normal range) in the first sample taken on arrival at an acute care hospital • Acid-base disturbance measured by lactate, base excess and pH level in first sample taken on arrival at acute care hospital. • Incremental cost of provision of the whole blood intervention; hospital resource use up to discharge or death, including ventilator days, days spent in critical care and total in-patient stay; health, social, and wider care service resource use to 90 days

		after injury; health-related quality of life (EQ-5D-5L) at 90 days after injury. • Thrombosis (arterial and venous thrombosis) up to 30 days after randomisation. • All transfusion reactions/events relating to pre-hospital blood components which have been reported to SHOT (Serious Hazards of Transfusion) in the first 14 days after randomisation.

[IV] randomisation is defined as the time that the trial box (containing intervention/control blood products) is opened by the Air Ambulance Service clinical team.

iv. FUNDING

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Air Ambulance Charities (listed in Appendix 1)	£322k
NHS Blood and Transplant	£322k
Ministry of Defence	£187k

v. ROLE OF TRIAL SPONSOR AND FUNDER

NHS Blood and Transplant (NHSBT) is the primary trial sponsor and overall management of the trial will be undertaken by the NHSBT Clinical Trials Unit. Queries relating to the NHSBT sponsorship of the trial should be addressed to: Yomi Adegbaju, National Research Manager, NHS Blood and Transplant, email: research.office@nhsbt.nhs.uk

The Sponsor has overall responsibility for the trial, including final financial decisions and participating in site monitoring visits.

The funders are NHS Blood and Transplant, the Ministry of Defence and participating Air Ambulance Charities. NHS Blood and Transplant and the Ministry of Defence will agree the trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results. Air Ambulance Services will agree the conduct of the trial and dissemination of the results with the Sponsor and Ministry of Defence.

vi. PROTOCOL DEVELOPMENT GROUP

Name	Affiliation	Authors' Contributions
Dr. Laura Green	NHS Blood and Transplant, Barts Health Trust and Queen Mary University of London	LG, JS, SS, GP, EB, TW, AW, RL and RC conceived and designed the study. LG, JS, JL and EL helped with implementation. HT and LS provided statistical expertise in clinical trial design and LS is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final version. Members of the NHSBT PPAG met twice prior to the trial submission, and have given valuable feedback which has informed the outcome measures, the consent process and the patient information documents.
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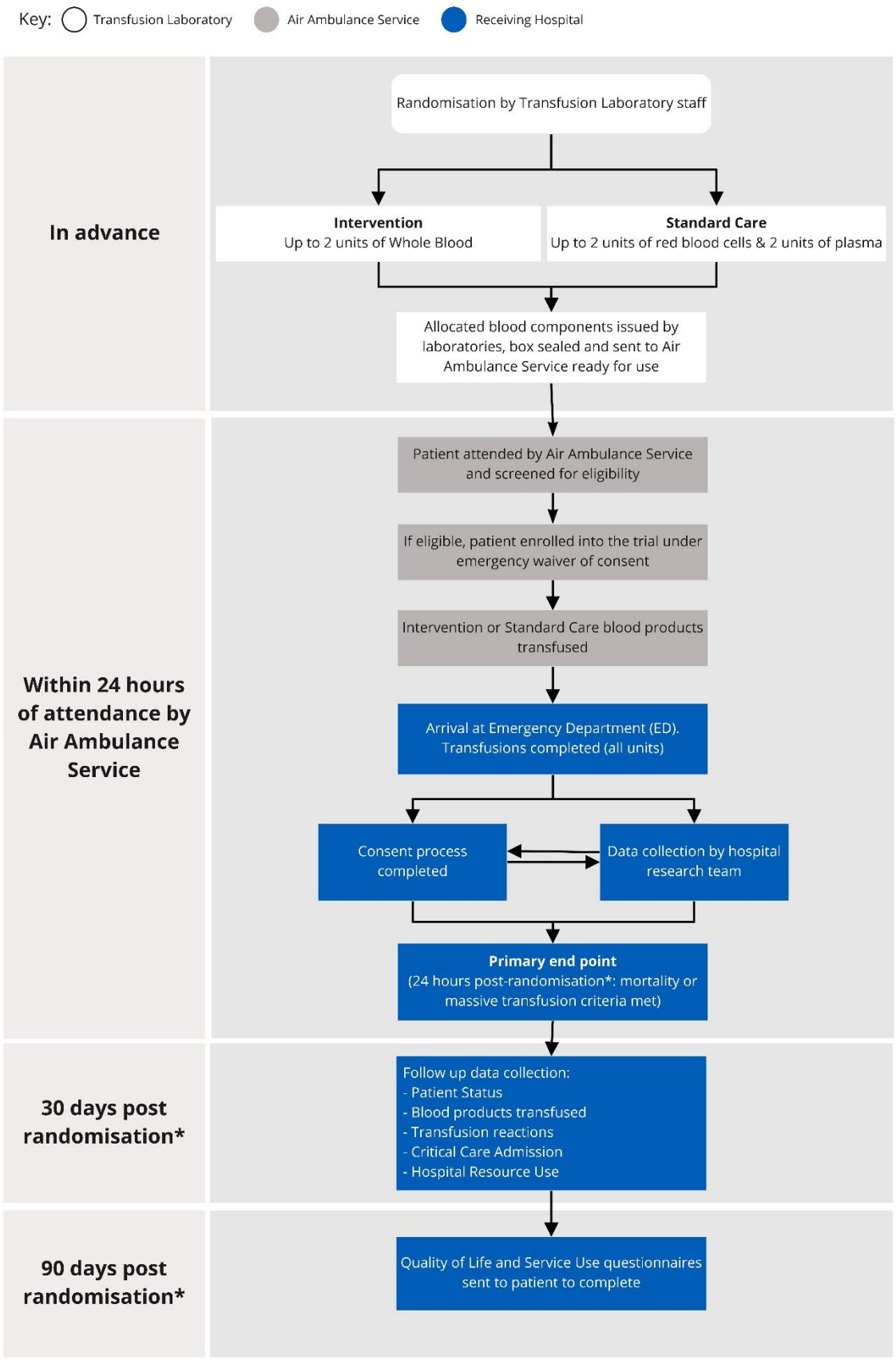
Members of the NHSBT Patient and Public Advisory Group (NHSBT PPAG)	NHS Blood and Transplant	

vii. KEY WORDS:

- Emergency medicine
- Major haemorrhage
- Transfusion

viii. STUDY FLOW CHART



*for the purposes of participant follow up, randomisation is when the sealed box of blood components is opened

ix. Study Schedule

Procedures	Transfusion Laboratory	On-Scene	ED Arrival	24 Hours Post-Randomisation	Day 30	Day 90
Preparing trial intervention boxes	X					
Confirmation of eligibility		X				
Emergency waiver of consent		X				
Open trial intervention box		X				
Transfusion: 2 x whole blood **OR** 2 x RBCs and 2 x Plasma		X				
Additional blood component transfusion (as required)		X				
Consent from participant / legal representative / Parent/Guardian			X	X	X	X
Record all blood components administered		X	X	X	X	
Follow-Up Data Collection*			X	X	X	
Serious Adverse Event reporting**		X	X	X	X	
Mortality		X	X	X	X	X
Acute Care Discharge Date				X	X	X
Hospital Resource Use (to discharge)					X	
Health, Social and Wider Care Resource Use questionnaire						X
Health-related Quality of Life questionnaire						X

Randomisation is defined as the time that the trial box (containing intervention/control blood products) was opened by the Air Ambulance Team.

*data collection timepoints are: Admission, 24 hours, Day 30, Day 90 (a summary of the data required at each timepoint is provided in section 9).

**SAE reporting timeframe is up to 14 days post-randomisation.

1. BACKGROUND

1.1 Burden of trauma and blood transfusion in pre-hospital

Major trauma kills more than 5,400 people every year in the UK (1) and globally more than HIV-AIDS, TB and malaria combined (2). Uncontrolled bleeding accounts for a significant proportion of these deaths, with approximately 20% occurring in the first 24 hours and 40% occurring within the first 30 days. Of the patients who survive to hospital, half require surgery and 80% require intensive care admission (3). Survivors have reported poor health-related quality of life, with negative effects on both physical and mental health (4) (5). The overall cost to NHS for managing major trauma is estimated to be £150 million per annum and blood transfusion treatment makes up around 12% of this cost (3).

Blood transfusion is a life-saving treatment in the management of bleeding patients until bleeding is controlled in hospital by surgery or interventional radiology. Blood transfusion is delivered through different blood components, namely red blood cells (RBC, important for carrying oxygen around the body), plasma (contains essential proteins to help blood clot) and platelets (small cells that are important for blood clot formation); all these components are derived from whole blood (WB) donation and are stored separately at different temperatures. WB is the complete package, as taken from a donor, and thus it contains all individual components in one bag, although the exact overall cellular content will not match that in individual components due to processing.

Observational studies in military (6) and civilian (7) settings have reported a 12-14% absolute reduction in 30-day mortality with pre-hospital RBC transfusion, with the effect being greater if transfusion is started within 15 minutes of medical evacuation (6). Hence, in the UK patients who are bleeding at the scene of an incident may be transfused blood before they arrive at hospital. However, the optimal transfusion strategy (whether this should be RBC only, RBC + plasma or RBC + plasma + platelets) in the pre-hospital setting has yet to be established and therefore across the country, transfusion practice varies. In a national survey in 2020, of the 18 Air Ambulance Services that responded (total of 22), 67% said that they administer red blood cells (RBC) and plasma, 22% administer RBC only and 11% give plasma only. None currently transfuse platelets pre-hospital.

1.2 Whole Blood

Carrying separate blood components to the scene of an incident, the current standard of care, introduces logistical challenges due to additional weight that the team needs to carry, and increased complexity as several bags need to be given to a single patient. Intravenous access may also be limited, and administering several components may potentially delay the transfer of patients to hospital (which could be detrimental to survival). Indeed, a recent cross-over major haemorrhage simulation study done as part of a pilot study in London, showed that transfusion of a combined component (red cells and plasma in one bag) significantly reduced time at scene (by 6 minutes) compared to transfusion of separate blood components, thus liberating the crews to deliver other time-critical treatment and moving patients quickly to hospital. Furthermore, transfusion of a combined component also required a fewer number of steps, fewer people and less equipment (article submitted for publication).

Transfusion of whole blood (WB) could overcome these logistical challenges. Another potential advantage of giving WB is the reduced donor exposure for patients, reducing the potential risk of infection or immunomodulatory complications. Furthermore, there is an argument that patients who are actively bleeding are losing 'whole blood' and quickly replacing all components lost with WB transfusion could improve survival. It is for these reasons that in the UK, as in many countries,

there is now increasing interest in providing WB transfusion for the resuscitation of bleeding patients outside hospitals, as WB contains platelets in addition to RBC and plasma.

In September 2016 the National Blood Transfusion Committee, which has a role in providing the framework on best transfusion practice to hospitals and blood services and advises the Chief Medical Officer on transfusion practice in the UK, requested that blood services prioritise the development plan for WB to enable faster administration of balanced resuscitation to patients who are bleeding in the pre-hospital setting.

WB was transfused routinely during the First and Second World Wars within 24 hours of it being donated (known as fresh WB). However, by 1965 the development of separated blood components with a longer shelf-life than WB enabled targeted replacement therapy for deficiency of clotting proteins with plasma (for haemophilia) or RBC (for anaemia), and in so doing it minimized the potential risks/side effects of receiving unnecessary blood components and made the logistics of supply and demand manageable for the blood manufacturing units. All of these contributed to the removal of (fresh) WB from routine practice.

NHS Blood and Transplant (NHSBT), the main blood supplier for hospitals in England, has demonstrated that WB with a longer shelf-life (21-days) can be manufactured for future use in the NHS. However, the costs of WB production are likely to be higher than RBC, as special leukocyte depletion filters are required to preserve the platelets within the WB. Moreover, donors required to support WB transfusion for pre-hospital patients would need to be of a specific type (i.e. male, group O, RhD negative, and have low titre for anti-A and B antibodies in plasma), since the recipient blood group is not known in advance of giving the transfusion. These donors are a precious resource and are required to support other groups of patients; therefore, it is important that this resource is utilised optimally.

1.3 Review of existing evidence on Whole Blood

Two systematic reviews, that compared the impact of WB transfusion versus blood component therapy on 24-hour and 30-day mortality for adult trauma patients with acute major haemorrhage, showed no clear benefit with WB transfusion (8), (9). In these reviews, there was only one randomised control trial (RCT, n=107 patients), which was not powered to demonstrate a difference in survival. Three observational studies reported no difference in 30-day mortality (n=830), while one study (n=354) showed a 13% decrease in 30-day mortality with WB transfusion (p=0.002) compared with component therapy (10). Regarding blood product use at 24 hours, the RCT showed that in a sub-group analysis of patients without severe brain injury this was lower in patients receiving WB than those who received component therapy (11 units vs. 16 units, p=0.02) (11). Similar results have been reported by other observational studies (10), (12), (13). None of these studies reported any transfusion related reactions with WB. However, higher rates of acute kidney injury and acute respiratory distress syndrome have been reported with the use of fresh WB (10), (13), but these have not been shown by other studies using the longer shelf-life WB component. Since the publication of these systematic reviews, another observational study in the USA comparing WB (similar to the UK WB component that will be used in this trial) with component therapy (RBC and or plasma) reported a two-fold increase in likelihood of 30-day survival with WB transfusion (odds ratio, 2.19; 95% CI 1.01-4.76; p = 0.047) (14).

Two recent trials have investigated the use of pre-hospital plasma resuscitation, showing conflicting results (15), (16). The combined data analysis from these trials suggests that the survival benefit is greatest in patients who received both RBC and plasma (17), in patients with blunt trauma (18), and

when pre-hospital times are longer (i.e. longer than 20 minutes) (19). A sub-study of the PROPRR (Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma) randomised trial suggests that trauma patients who received early platelets had an 11% reduction in 24 hour and 30-day mortality (20).

Wastage of unused blood products is a concern. If WB is reserved for one group of patients (in the pre-hospital environment) it is likely that the component wastage will be high unless it is also given to other patients who are bleeding in hospital (as is done for other blood components).

A systematic review conducted in preparation for this study assessed whether there is a difference in safety outcomes with the transfusion of WB compared to blood components for any bleeding patient regardless of age or clinical condition. We identified six RCTs (618 participants) of which only one was a trauma trial (n=107), and five were surgical non-trauma trials (n=511). The evidence for all trials was graded as low. There was no evidence of a difference in mortality of patients receiving WB compared to blood component therapy, although there was a reduction in the duration of oxygen dependence (1 study; n=60; mean difference 5.9 fewer hours [95% CI -10.83, -0.99] in the WB group), and a reduction in hospital stay (1 study, n=64, median difference 6 fewer days in the WB group). For the remaining outcomes (organ injury, mechanical ventilation and intensive care unit requirement, infection, arterial/venous thrombotic events, and haemolytic transfusion reaction) there was no difference between WB and component therapy (21).

1.4 Assessment and management of risk

The main potential advantage of WB is that it contains all components in one bag and therefore it may be perceived to be better than separate blood component therapy for resuscitation of major bleeding patients, particularly outside hospital settings. However, the evidence of enhanced effectiveness versus the current standard of care is limited. When compared to blood component therapies, several systematic reviews have shown that the safety profile of WB transfusion is comparable to the blood component therapy (8), (9), (21).

There is therefore no evidence to suggest that WB transfusion results in higher risk to the patient than the current standard of care, although we will monitor this during the trial.

2. RATIONALE

Early blood transfusion improves survival in patients with life-threatening bleeding, but the optimal transfusion strategy in the pre-hospital setting has yet to be established. Although there is some evidence of benefit with the use of WB, there have been no RCTs exploring the clinical and cost effectiveness of pre-hospital administration of WB versus component therapy for bleeding trauma patients in the UK setting (8).

For traumatic haemorrhage in the pre-hospital setting, the recent updated British Society for Haematology (BSH) guideline acknowledges the need for early haemostatic resuscitation with RBC and plasma, as long as it does not unduly add to transport time.

In 2020 we conducted a survey of UK Air Ambulance Services (18 of 22 services responded). In this survey, 82% stated that WB would be their preferred component followed by leukocyte depleted red cells and plasma in one bag (65%), and RBC + thawed FFP + platelets (30%). All those who responded said that they would like to see an RCT conducted before the wider implementation of

WB in the NHS. In a stakeholder meeting in July 2020, with representatives from all Air Ambulance Services in the UK, most participants stated that they would support a clinical trial.

Therefore, it is essential for patients, healthcare professionals and blood services that the clinical and cost effectiveness of pre-hospital WB transfusion is evaluated in a large trial before its widespread implementation in the NHS. A national programme of WB production would necessitate significant changes in the current manufacturing processes for blood services, in order to provide appropriate support for hospitals. WB production could potentially affect the supply of blood components required to treat other patients, as a unit of WB cannot be used to manufacture other components. However, it could also be argued that early transfusion of WB may reduce the need for further blood component transfusion when patients arrive at hospital, due to earlier control of bleeding. The proposed study would enable us to evaluate all these uncertainties.

Patient and public involvement has been sought through the NHSBT Patient and Public Advisory Group (PPAG). The trial proposal was presented in August 2020, and their feedback guided the development of the proposal. Specifically in relation to the follow-up timepoints, and the consent procedures now described in section 7 of this protocol. For example, the PPAG felt strongly that relatives of deceased patients should not be approached for consent. The team consulted with the PPAG again in January 2022, after which the PPAG then reviewed the patient information documents and their feedback has been incorporated into the final versions. In addition, there are two independent patient/lay representatives on the Trial Steering Committee.

3. OBJECTIVES AND OUTCOME MEASURES

3.1 Primary objective

The primary objective is to determine whether pre-hospital leukocyte-depleted whole blood transfusion is better than standard care (component transfusion) in reducing the proportion of participants who experience death or massive transfusion at 24 hours.

3.2 Secondary objectives

The secondary objectives are to determine:

- All-cause mortality at 6 hours, 24 hours, 30 days and 90 days
- Morbidity up to 30 days: ie. number of organ failure free days (see definitions under section 3.4), and number of days in critical care and in hospital.
- Hospital resource use up to 30 days, discharge or death, including organ failure free days, time spent in critical care and total in-patient stay, blood components and additional haemostatic agents received
- The cost-effectiveness of pre-hospital whole blood administration versus standard care for traumatic haemorrhage
- Health-related quality of life at 90 days
- Health, social and wider care resource use up to 90 days
- Safety

3.3 Primary Outcome Measure

The primary outcome measure is the proportion of participants with traumatic haemorrhage who have died (all-cause mortality) or received a total of 10 or more units of any blood components in the first 24 hours from randomisation[IV].

[IV]A participant is considered randomised and entered into the trial when the trial intervention box has been opened.

3.4 Secondary Outcome Measures

3.4.1 Clinical Outcomes

- Individual components of the primary outcome: Proportion of participants who:
    - Experienced all-cause mortality at 24 hours from randomisation.
    - Received a total of 10 or more units of any blood components in the first 24 hours of randomisation [IV].
- All-cause mortality within 6 hours and separately 30 and 90 days of randomisation [IV].
- Number of organ failure free days up to 30 days after randomisation, defined as the number of days free of advanced cardiovascular, advanced respiratory and advanced renal support. Each component of organ failure free days will also be reported separately:
    - Number of days free of advanced respiratory support
    - Number of days free of advanced cardiovascular support
    - Number of days free of advanced renal support
- Days in critical care and separately in an acute care hospital (up to 90 days).
- Units of each blood component received in the 24 hours after randomisation [IV] (including prehospital transfusions): WB, RBC, plasma, platelets and cryoprecipitate.
- Amount of cell salvage received at 24 hours (in mLs) after randomisation [IV].
- Number of participants receiving additional haemostatic agents received at 24 hours after randomisation [IV]: recombinant Factor VIIa, fibrinogen concentrate, prothrombin complex concentrate (PCC), tranexamic acid (TXA).
- Presence of coagulopathy (defined as prothrombin time above the limits of a normal range) in the first sample taken on arrival at an acute care hospital.
- Acid-base disturbance measured by lactate, base excess and pH level in first sample taken on arrival at acute care hospital.

[IV]A participant is considered randomised and entered into the trial when the trial intervention box has been opened.

3.4.2 Cost-Effectiveness Analysis Outcomes

- Incremental cost of the whole blood intervention.
- Hospital resource use to discharge or death.
- Health, social and wider care resource use to 90 days after randomisation.
- Health-related quality of life as measured by EQ-5D-5L at 90 days after randomisation [IV].

[IV]A participant is considered randomised and entered into the trial when the trial intervention box has been opened.

3.4.3 Safety Outcomes

- Thrombosis (arterial and venous thrombosis) up to 30 days after randomisation.
- All transfusion reactions/events relating to pre-hospital blood components which have been reported to SHOT (Serious Hazards of Transfusion) occurring in the first 14 days after randomisation.

4. TRIAL DESIGN

A multicentre, pragmatic, superiority, randomised controlled, open-label, parallel group two arm trial with internal pilot and within-trial cost-effectiveness analysis.

5. TRIAL SETTING

Air Ambulance Services: responsible for treating patients on scene and delivering the trial intervention prior to hospital admission. These sites will be Air Ambulance services that deliver a combination of RBC and plasma as standard care for the treatment of life-threatening bleeding. The study will also be open to services that deliver advanced pre-hospital emergency care and blood transfusion via land vehicles.

Transfusion Laboratory Sites: responsible for supplying blood components in accordance with the randomisation procedure. These sites are the hospitals (Transfusion Laboratories) which supply blood components to the participating Air Ambulance services. For Air Ambulance Services (AAS) that use freeze-dried plasma (LyoPlas), this can either be procured directly by the AAS or via the Transfusion Laboratory.

Receiving Hospital Sites: secondary care sites where participants will be admitted following trial treatment. These sites will be designated Major Trauma Centres, Trauma Units, or other hospitals that receive participants from the participating Air Ambulance Services.

There will be some overlap between the Transfusion Laboratory Sites and the Receiving Hospital Sites.

6. ELIGIBILITY

The pragmatic nature of this trial means that the decision to administer the intervention will be based on clinician judgement and according to the AAS usual criteria for initiation of blood transfusion. As injured children and adults are routinely managed by Air Ambulance Services and may receive pre-hospital blood transfusion, patients of all ages will be included in the study.

6.1 Participant Inclusion Criteria

- Patient (of any age) who has suffered a traumatic injury.
- Attended by a participating Air Ambulance Service clinical team.
- Requires pre-hospital blood transfusion to treat major traumatic haemorrhage.

6.2 Participant Exclusion Criteria

- No intravenous or intraosseous access (should be assessed prior to opening box).
- Knowledge that patient will object to being given blood transfusion for any reasons.
- Blood already administered on-scene, prior to arrival of the participating AAS.

6.3 Patients with Non-Traumatic Haemorrhage

There is no evidence to support pre-hospital blood transfusion for non-traumatic clinical causes of bleeding, and current national major haemorrhage BSH guidelines (22) and the revised guideline (submitted for publication in Jan 2022) do not recommend its use.

If blood products are administered in extremis to non-trauma patients in the context of this trial by participating Air Ambulance Services (as the trial intervention may be the only blood products carried), these patients will be withdrawn from the trial once they arrive at the acute care centre, excluded from the analyses and replaced in the overall sample size. In a national survey of practice, over a one-year time period (2020), there were 20 patients who were given blood components by an AAS to treat a non-traumatic haemorrhage, and hence we anticipate that this will be a rare occurrence in the trial.

7. CONSENT

7.1 Participant identification

Potential participants will be identified by the attending AAS clinicians on-scene by use of the eligibility criteria. The decision to enroll the patient will be the responsibility of the treating clinician.

7.2 Screening

A screening log will be completed by participating AAS which will record all patients considered for eligibility for enrolment in the trial and capture the reason(s) that patients were not enrolled or were missed. The log will include date the patient was considered for enrolment in the trial, patient age, sex, inclusion/exclusion criteria and other reasons for non-enrolment. The screening log data will be reviewed at regular intervals by the Trial Management Group.

7.3 Co-enrolment

Due to the emergency nature of this trial, it is highly unlikely that those enrolling participants to SWiFT will be aware if a participant is already enrolled in a clinical trial. Where a SWiFT participant is subsequently found to have been participating in a concurrent trial or is being considered for enrolment into another trial, the site must notify the SWiFT CIs, who will in turn liaise with the CI for the other trial to determine whether co-enrolment is permitted.

7.4 Consent

Major traumatic haemorrhage is a life-threatening condition that requires urgent treatment. The vast majority of participants will lack capacity and/or will be minors of unknown age. Due to the emergency nature of major trauma time will not allow for written informed consent to be obtained first from a person with parental responsibility (in the case of minors) or a legal representative for incapacitated adults before randomisation into the trial.

It is expected that participants will lack capacity throughout the recruitment and intervention periods of the trial and although an occasional participant may retain capacity, their clinical condition will require immediate treatment. It would be inappropriate to attempt to gain informed consent at this time, as it could delay life-saving treatment. It would also be clinically unjustifiable to delay treatment until full informed consent can be obtained from a personal legal representative or parent/guardian. Even if such a representative or person with parental responsibility were immediately available, the emotional distress of the situation is such that they would be unlikely to make an informed decision in the minimal time available. Furthermore, sudden traumatic injury cannot be predicted or foreseen, and there is no opportunity to seek consent in advance. Consequently, SWiFT cannot be conducted on the basis of prospective informed consent. Participants will be enrolled under an emergency waiver of consent.

Participants who are incapable of giving consent in emergency situations are an established exception to the general rule of informed consent in clinical trials. This is acknowledged in the Declaration of Helsinki, 2013. Under UK law (The Medicines for Human Use (Clinical Trials: Amendment No. 2) Regulations 2006) minors or incapacitated adults in emergency settings can be entered into a trial before informed consent is obtained provided that:

- Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency.
- It is not reasonably practicable to obtain informed consent prior to entering the subject (due to the extreme physiological compromise which will be present in eligible participants, it is not practical to seek informed consent as to do so would delay resuscitation and increase the risk to the potential participant's life).
- The action to be taken is carried out in accordance with a procedure approved by the Research Ethics Committee. The consent procedure will be described in this protocol (7.4.2, 7.4.3).

Contact with trial participants and/or their relatives/friends/person with parental responsibility to initiate the consent process will be made as soon as practically possible after the initial emergency has passed, taking the utmost care and sensitivity in doing so. Based on findings from previous trauma research studies and from engaging with patient and public representatives it has been suggested that the earliest practicable time to make contact is once the participant is no longer critically ill (process should be started within 72 hours).

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the participant information sheet (PIS) given to the participant or their legal representative or parent/guardian, version number of the informed consent form (ICF), what type of consent was received (legal representative and/or participant, or parent/guardian), and that the ICF was signed and dated. The participant will have the right to withdraw at any point without impact on their ongoing care – this is made clear within the patient information documents.

Throughout the follow-up period, the participant's willingness to continue in the trial will be ascertained (through the participant themselves, or their legal representative or parent/guardian as appropriate) and documented in the medical notes, and the participant or their legal representative / parent/guardian will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the decision to continue, participants or their legal representative / parent/guardian will be given time to consider and if happy to continue will be re-

consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

With the consent of the participant / legal representative / Parent/Guardian, the participant's General Practitioner (GP) will also be informed that they are taking part in the trial.

7.4.1 Participant Consent (*after* trial intervention)

This section is relevant to participants aged ≥ 16 years.

The local Research Team at the receiving hospital will assess if the participant has capacity to consent for themselves. If the participant does have capacity, they will be provided with the Research Ethics Committee (REC) approved PIS explaining the trial and the options of their continued involvement. The participant will be given time to consider the information, have the opportunity to ask questions and discuss with others. A member of the local Research Team will ask the participant when they would like someone to come back to discuss participation further and potentially receive consent.

The participant may decide that it is not an appropriate time to discuss the trial, or they may decide upfront that they do not want to be involved, in which case their feelings will be respected and their decision about continuing in the trial will be recorded. Where consent is withheld, the participant will be withdrawn from the trial; data collected up to that point will only be retained with the consent of the participant or legal representative / parent/guardian.

A summary of the consent process for adults (aged ≥ 16 years) is shown in Appendix 2.

7.4.2 Participants Who Lack Capacity to Consent for Themselves

For adult participants (aged 16+) who lack capacity:

As soon as practically possible after randomisation (normally within 72 hours), a personal legal representative for the participant will be identified and approached, given an information sheet and asked to provide their informed consent for the participant to remain in the trial. If the participant remains incapacitated and a personal legal representative is not available, or if approaching the personal legal representative is likely to induce a delay or it is deemed by the research team to be inappropriate to approach the personal legal representative, consent from a professional legal representative will be sought. In this study, a professional legal representative is defined as a clinician (qualified doctor or registered nurse) with appropriate training (according to local Trust policies) to take on the role of professional legal representative. A professional legal representative should be a person who is directly involved in the participant's care but who is not connected to the conduct of the trial (and not listed on delegation of duties log). If no such person exists a person can be nominated by the healthcare provider, each participating site will therefore formally document and appoint a named professional legal representative(s) at the start of the trial who will be made aware of the aims of the study and know what the intervention is.

Sites should obtain the consent of a legal representative as soon as possible after randomisation to enable continued collection of data should the participant be discharged/self-discharge/transferred to another NHS Trust before the Research Team can approach the participant and/or personal representatives for consent.

Research Teams should periodically check the capacity of the participant following admission to hospital. If a participant regains capacity, they should be approached directly for consent (following procedure described in section 7.4.1). **The participant's wishes (consent or refusal) will supersede the consent of the personal or professional legal representative**. Where consent is withheld, the participant will be withdrawn from the trial; data collected up to that point will only be retained with the consent of the participant or legal representative.

If the participant does not regain capacity, a personal and/or professional legal representative's consent is sufficient for the participant to remain in the study for the ongoing collection of follow-up data.

Examples of common consent scenarios

- The patient is incapacitated and has no-one who can provide consent as a legal representative
  The research team should obtain professional legal representative consent for the patient as soon as possible

- The research team has approached a personal legal representative, but before consent is obtained, the patient dies
  The research team should not approach the personal legal representative to complete the consent process.

- The research team has not had time to approach the personal legal representative before the death of the patient
  The research team should not approach the personal legal representative due to the likely distress it would cause.

- If a personal legal representative is unlikely to be able to consent within 5 days
  The research team should obtain consent from a professional legal representative

- The patient regains capacity and self-discharges before an approach can be made for consent
  The research team should attempt to contact the patient at home (a maximum of 3 attempts)
- The patient is discharged into police custody or the custody of HM Prison Service before an approach for consent can be made
  The research team should obtain consent from a professional legal representative

- The patient is transferred to another hospital Trust for continued treatment (before or after consent)
  Please contact the Clinical Trials Unit to inform them that the patient has been transferred to another hospital Trust, the name of the new treating hospital and their consent status.

7.4.3 Consent Arrangements for Participants under the Age of 16

Under Clinical Trial Regulations (which apply to CTIMPs), a person under the age of 16 years is deemed to be a 'minor' and an appropriate adult* must give consent for that child to take part in the trial. If the participant has capacity, they will also be asked to provide assent for their continued participation in the trial.

Appropriate adults who are able to give consent on behalf of minors are:

- Parent (agreement of only one parent is required) or someone with parental responsibility (eg local authority with parental responsibility for that child).
- Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the child/young person, and is available and willing to do so. A legal representative should only ever be approached if someone with parental responsibility cannot be contacted. If a personal legal representative is not available:
- Professional legal representative i.e. a doctor responsible for the medical treatment of the child / young person if they are independent of the study, or a person nominated by the healthcare provider.

As soon as practically possible after admission, an appropriate adult will be identified according to the hierarchy above. The adult will be approached, given an information sheet and asked to provide their informed consent for the participant to remain in the trial.

Research Teams should periodically check the capacity of the participant following admission to hospital. If a minor regains capacity, and it is practical and appropriate to do so, the child's assent will be sought for their continued participation in the trial. Minors will be given age-appropriate material (6-10 years and 11-15 years) with information about the trial, which is understandable to them and which explains what is involved. If the child or young person expresses a refusal to take part or desire to withdraw these wishes must be considered.

A summary of the consent process for minors (aged < 16 years) is shown in Appendix 3.

7.4.4 Additional Consent Considerations

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Where the participant cannot read or write, or has a cognitive or physical impairment, appropriate alternative methods for supporting the informed consent process should be employed at site. This may include consent to be taken verbally, in the presence of at least one witness who must sign the consent form as evidence that the information was accurately explained to and understood by the participant and that consent was freely given. This may be necessary in the case of problems with reading or writing, or bilateral arm injuries. If the participant and/or personal legal representative does not understand English sufficiently to understand the trial and what is involved, a translator will be used from family, friends, a hospital language interpreter or translation service.

The right of a participant to refuse participation without giving reasons will be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment and must be provided with a contact point where they may obtain further information about the trial. Data collected up to the point of withdrawal from the trial will be retained and used if agreed by the participant.

In exceptional circumstances, it may not be possible to obtain informed consent (either via the participant directly, or via a personal/professional legal representative) before a participant is discharged from hospital. If no contact with the participant is possible, we will use the data that has previously been collected under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group).

Electronic consent can be used in this trial and a PDF version of the consent forms are available for sites. The HRA permits the use of a simple typed electronic signature for Class A CTIMP trials. The use of the Pando App (https://network.hellopando.com/nhs/) to transfer consent forms is approved at sites.

7.4.5 Participants Who Do Not Survive

One of the most challenging ethical considerations of this trial relates to the inevitable death of some participants. Actively seeking out and informing relatives of trial participation is transparent and avoids potential distress were the family to discover at some future point that their relative had been involved in a research trial. However, informing the family of trial participation in the immediate aftermath of their relative's death will impose an additional emotional burden at a time of great distress. Previous and ongoing emergency care studies have used passive information approaches, placing information in publicly accessible locations and in sites likely to be visited by relatives of the deceased (hospitals, GP surgeries, the offices of the Registrars of Births and Deaths). Such information contains brief details of the trial and contact details for those wishing to seek further information about the trial. This allows a relative to make an individual decision as to whether to seek further information as to whether their relative was part of the trial, at a time of their choosing. This is the approach that we will take with the SWiFT trial and a REC approved poster will be placed in appropriate locations at receiving hospitals (i.e. the bereavement office).

For those participants that have been randomised, but subsequently die either at scene or *en route* to hospital, it will be impossible to obtain any form of consent. In these situations, the AAS clinical team will be responsible for completing the relevant Case Report Forms.

7.4.1 Participants Transferred to Non-Participating Hospitals

There may be some situations where due to the geographical location of the participant or the severity of their injuries, the AAS clinical team will transfer participants to non-SWiFT hospitals. This may be temporary (e.g. to be stabilised before being transferred to a SWiFT hospital), or the participant could remain at a non-SWiFT hospital permanently for follow-up or end-of-life care (if further treatment is considered futile).

If the participant is initially stabilised at a non-SWiFT hospital but is then subsequently transferred to a SWiFT hospital, the Research Team at the SWiFT hospital will complete the consent process and request relevant data.

If a participant is transferred to a non-SWiFT hospital and remains there (for follow-up care, or if they subsequently die), the SWiFT Trial Office will request a minimal data set via the Admission Form and Exit Form, as these forms capture data pertaining to the composite primary outcome measure.

8. RANDOMISATION

8.1 The Randomisation Scheme

A restricted randomisation method will be used in this trial. It will consist of randomly permuted blocks of varying undisclosed sizes, and stratified by AAS, to account for variation in trauma care and type of trauma between delivery sites. There will be a 1:1 allocation ratio, to the intervention and control arms. The allocation sequence will be produced from a specification provided by the trial statistician to Sealed Envelope (a centralised web-based randomisation service) and quality checked by the trial statistician.

8.2 Method of Implementing the Randomisation Sequence

Allocation will be conducted by the participating Transfusion Laboratory teams using Sealed Envelope. Only Sealed Envelope and the trial statisticians will have access to the randomisation list.

Upon randomisation, an email notification will be sent to the Transfusion Laboratory Team and NHSBT CTU, which will include the randomisation number (of the form RXXXX), date and time of randomisation and the allocated treatment (whole blood or standard care). The randomisation number must be added to the trial box and will be used on all subsequent study documentation.

Using the randomised allocation, boxes of blood components will be prepared by the participating Transfusion Laboratory teams.

8.3 Role of Transfusion Laboratories

The role of hospital transfusion laboratories in the trial will be to maintain a constant supply of randomised trial interventions to the AAS clinical team. The transfusion laboratories will obtain the randomised allocations via the Sealed Envelope online system. Unique log-in usernames and passwords will be provided to the transfusion laboratory staff supporting the trial.

RANDOMISATION

To perform a randomisation, please visit www.sealedenvelope.com/access.

Transfusion laboratories will be supplied with pre-printed 'SWiFT randomisation number' labels to which they will add by hand the randomisation number. A registered user at the transfusion laboratories will perform a unique randomisation for each box to be used by the AAS. The allocated trial intervention will be packed into transport boxes, ensuring that the randomisation number is clearly documented on the outside of the box. The date and time of expiry will also be written on each transport box. The packed, sealed transport boxes will be dispatched to the AAS using an established courier service as required for each site. Unused boxes should be returned to the transfusion laboratory and if unopened replaced "like-for-like". A new randomisation should only be performed once the box has been used (i.e. contents have been transfused to a participant) or if the box was returned opened but the contents were not used.

8.4 Role of Air Ambulance Service Clinical Teams

AAS clinical teams should ensure that they have one trial intervention box available on each of the vehicles during each attendance. Additional standard care components can be carried, as vehicle

capacity allows. Each trial box will be labelled with a randomisation number of the form RXXXX. The Pre-Hospital Form should be completed for every participant who receives blood components from a trial box. A participant is considered randomised at the time that the trial box has been opened (seal broken).

Unopened boxes (with seal still intact) should be returned to the Transfusion Laboratory prior to expiry. The standard care components (red blood cells and fresh frozen plasma) may be returned to stock and re-issued if there have been no temperature excursions.

8.5 Blinding

The transfusion laboratories will be notified of the treatment allocation when they perform the randomisation, though must keep this information confidential and not reveal the information to anyone except NHSBT CTU.

AAS clinical teams are blinded to the randomised allocation until the trial box is opened, after which point it is not feasible to maintain blinding. To ensure that the team can remain blinded until the box is opened, the boxes containing intervention or control, will be the same size and shape. It is not possible to blind the team at the receiving hospital to the intervention.

Participants will be blinded to allocation until the trial box is opened, but they may discover this information post-randomisation (e.g. by reading their medical notes or requesting this information from the Research Team), although there is no obligation to inform the participant which treatment they received.

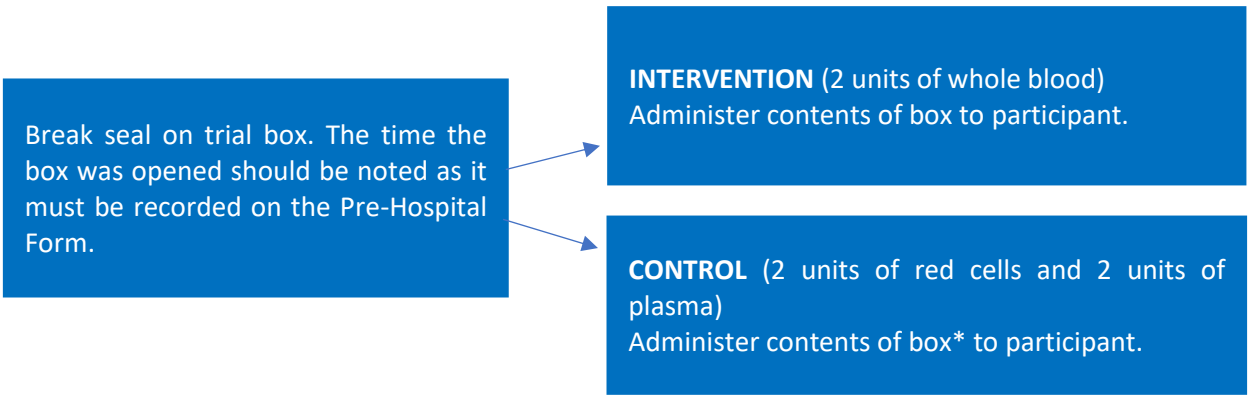
Since the components of the primary outcome measure are objective, we believe that the unblinded nature of this trial will not compromise its scientific validity.

Throughout the duration of the trial, only the trial statisticians and DMC will see accumulating trial data by arm. Everyone else will remain blinded to this information until the final trial results are available.

9. TRIAL PROCEDURES AND ASSESSMENTS

9.1 On-Scene

For all patients who have suffered a traumatic injury and require pre-hospital blood transfusion for major haemorrhage:



*If using freeze-dried plasma (LyoPlas), this may be held separately from the trial box.

If bleeding continues and further fluid resuscitation is needed, additional blood components can be administered as per standard care and as required, following the initial trial components.

All blood components should be given according to local standard practices on the use of blood warmers.

9.2 On Arrival at the Receiving Hospital Emergency Department

On arrival at hospital the AAS clinical team will hand over clinical responsibility for the participant to the receiving hospital team and complete the Pre-Hospital form (on the eCRF). If the trial intervention has not been completed by the time the participant arrives in hospital, it should be completed after arrival at hospital if is still clinically indicated. Further management is dictated by normal clinical protocols. Each unit of blood administered pre-hospital must be recorded on the eCRF, along with the donation number (G number) of the unit and the transfusion start time.

The PI and Research Team at the receiving hospital will be responsible for initiating the consent process (as detailed in section 7.4) and for the follow-up data collection for trial participants.

The first available prothrombin time, lactate, pH, base-excess (i.e. from first blood samples taken after admission as part of routine standard care) should be recorded. No additional blood sampling is required.

The transfusion laboratory at the receiving hospital will be responsible for recording the final 'fate' of all blood components that were administered to the participant, to ensure full traceability.

9.3 Follow-Up Assessments

9.3.1 Day 1

Data to be collected by Research Team (at 24 hours post-randomisation):

- Participant's demographics and baseline data (please see section 12.3.1)
- Participant status (alive/dead) at 6 hours and 24 hours. If participant has died, the Exit Form must be completed to provide further detail.
- Total number of blood components transfused (i.e. WB, RBC, FFP, cryoprecipitate, platelets).
- Cell salvage / autologous blood transfusion.
- Haemostatic agents received: recombinant Factor VIIa, fibrinogen concentrate, prothrombin complex concentrate, tranexamic acid.

9.3.2 Day 30

Data to be collected by Research Team (at 30 days post-randomisation):

- Participant status (alive/dead). If participant has died, the Exit Form must be completed to provide further detail. If research teams are unable to confirm the participant's status from hospital records, teams should approach the patient's GP in order to ascertain this. A copy of the consent form should be provided to the GP.
-
- Total number of blood components transfused (i.e. RBC, FFP, cryoprecipitate, platelets).
- Critical Care admission (yes/no), plus date/time of admission where applicable.

- Hospital Resource Use (up to discharge from acute care hospital or death (whichever is first)).
- Thromboembolic events (clinically diagnosed).
- Check for any transfusion reactions which have been reported to SHOT (occurring in first 14 days post-randomisation).

9.3.3 Day 90

For participants that are alive at Day 90 post-randomisation:

- Participant status (alive/dead). If participant has died, the Exit Form must be completed to provide further detail.
- Health-Related Quality of Life (EQ-5D-5L) questionnaire should be sent to the participant for completion (EQ-5D-5Y should be used for participants aged 5-14 years).
- Health, Social and Wider Care Service Use questionnaire should be sent to the participant for completion.

If a participant shows signs of extreme anxiety and/or depression from the Health-Related Quality of Life questionnaire, the research team at the receiving hospital should contact the participants' General Practitioner. A template letter is provided for sites to use.

9.4 Participant Transfers

If a participant is transferred to another participating trial site, the responsibility for ongoing data collection should reside with the PI/Research Team at the new hospital.

If a participant is transferred to a non-participating site, the Research Team should request the required data from the new hospital.

9.5 Loss to Follow-Up

A participant will be considered lost to follow-up for the day 90 data collection if 3 attempts to contact the participant or their legal representative or parent/guardian have been made and there is no response, and the research team has been unable to confirm their survival status via their GP.

9.6 Withdrawal criteria

With the exception of non-traumatic haemorrhage cases (please see section 6.3), participants will not be replaced as the sample size calculation (see section 12.1 for full details) allowed for 5% drop out. The drop-out rate will be monitored by the TMG throughout the trial, and specifically by the DMC at the first interim analysis. If this rate increases above 5%, then consideration to increasing the sample size calculation will be required.

It will be extremely rare that participants are withdrawn between randomisation and the delivery of the intervention, as this period is very short (typically less than 5 minutes), or during the intervention (as it is only given once during the trial).

With the exception of cases where consent is withdrawn or if the participant has a non-traumatic haemorrhage, there are no other specific circumstances where a participant should be withdrawn from the trial. If a participant is withdrawn, a withdrawal form should be completed which will detail the reason for withdrawal, whether we're able to keep and use the data we already have.

9.7 Data Linkage

Patient identifiable information (date of birth, NHS number) will be collected in order to link with other sources, as listed below. This prevents duplicate data collection and reduces the burden of data collection for hospital research teams.

Source:	Data to be obtained:
Intensive Care National Audit and Research Centre (ICNARC)	Organ failure free days (defined according to the critical care minimum data set), length of stay in critical care
Trauma Audit and Research Network (TARN)	Initial vital signs, injury characteristics (abbreviated injury scale (AIS), interventions, injury severity score (ISS) and probability of survival (Ps)).

A submission to TARN will be made for all participants who have been enrolled into the SWiFT trial and have been admitted to hospital alive.

9.8 End of Trial

The End of Trial is defined as the date when follow-up data is completed for all participants.

10. TRIAL INTERVENTION

The trial will compare up to 2 units of whole blood (intervention arm) versus up to 2 units of red blood cells and 2 units of plasma (control arm). Following this, additional blood components should be administered as required (as per standard of care).

10.1 Intervention Arm (whole blood)

The WB component will be manufactured by NHS Blood and Transplant, which is the main blood supplier of blood in England.

The WB units are derived from a single donor after the WB is collected into 66.5 mL citrate-phosphate-dextrose (CPD) anticoagulant (see table in section 10.3 for volumes) and filtered to remove the white cells as a variant Creutzfeldt–Jakob disease (CJD) safety measure step that is applied to all blood components manufactured in the UK since 1999.

Once manufactured, the WB units will be transported to hospitals under continuous temperature control as per standard operating procedures and stored in the transfusion laboratories at 2 – 6 °C for up to 21 days.

The WB units will be group O, RhD negative, high titre negative for anti-A and anti-B, and Kell negative. The total volume of WB units is 470 mL, of which anticoagulant volume is 60 mL.

10.1.1 Handling of Whole Blood

The handling of WB units in hospitals will comply with the Blood Safety and Quality Regulations (BSQR) UK. In addition to the trial safety reporting procedures, hospital staff will be responsible for reporting all transfusion-related adverse events/reactions via Serious Hazards Of Transfusion and Serious Adverse Blood Reactions and Events (SHOT/SABRE) according to standard procedures (as

required under the regulations of the Blood Safety Quality Regulations UK 2005.The MHRA are the competent authority for monitoring BSQR.

The BSQR imposes significant requirements on the whole transfusion practice from laboratory to clinical areas, and vice versa. As a result, transfusion laboratories have standard operating procedures for:

- storage, distribution and transport of blood and blood components within the hospital.
- temperature controlled storage, its monitoring and management of the "cold chain".
- validation and calibration of processes and equipment.
- notification of serious adverse events and reactions

Any unused units will be disposed of in accordance with local requirements. For used products, all hospital transfusion laboratories are required by BSQR to keep the evidence of traceability for every unit used (or wasted) for 30 years. The following data items will be electronically recorded:

- Donation number
- Component type
- Blood establishment which provided the blood component
- Date provided
- Identity of patient who received the blood component or final fate if not transfused

Further, transfusion laboratories have SOPs in place that accurately, efficiently and verifiably withdraw blood and blood components involved in serious adverse events or reactions or that are judged to have the potential to cause harm to patients. All these steps will be used to recall WB units if necessary.

10.2 Control Arm (red blood cells and plasma)

The control arm will consist of 2 units of RBC and 2 units of plasma (either thawed fresh frozen plasma or freeze-dried plasma (LyoPlas), dependent on the standard practice for each AAS).

RBC and FFP are blood components that are supplied by NHS Blood and Transplant (from national stocks), to the hospitals that are supporting this trial.

LyoPlas is a freeze-dried plasma product derived from a single donation and is licenced for use in the same indication as fresh frozen plasma. LyoPlas is licensed for use in Germany as a medicinal product under Marketing Authorisation Number PEI.H.03075.01.1 and is therefore being classified as an Investigational Medicinal Product in the SWiFT trial.

10.3 Summary of Blood Components

	Red blood cells in additive solution (RBC)	Fresh-Frozen plasma (immediately once thawed) (TP)	Cryoprecipitate (pool of 5 donations) (Cryo)	Platelet concentrate (buffy coat derived) stored in 65% PAS (PLT PAS)	Platelet concentrate (apheresis) stored in plasma (PLT plasma)	Whole blood, LD (WB) – platelet replete**
Total volume (mL)	289 ± 31.4*	263 ± 16.8*	230 ± 10.2*	294 ± 12.1*	219 ± 13.5*	470 ± 3.4
Volume of anticoagulant (mL)	4.3	56.9	49.6	22.2	30.4	59.8
Citrate (mmol/unit)	0.385	5.088	4.435	1.985	2.275	5.348
Volume of additive solution (mL)	105	n/a	n/a	200	n/a	n/a
Volume (mL) of 'pure' red cells	164	n/a	n/a	n/a	n/a	179

*values obtained from NHSBT Quality Monitoring data January-March 2020 (23). Where applicable, values shown are mean ± SD. All other values calculated from mean of constituent values.

10.4 Preparation and Labelling of Intervention

Blood components (WB, RBC, FFP) will be prepared, labelled and issued by NHSBT as per standard operating procedures.

For AAS that carry freeze-dried plasma (LyoPlas), this should be sourced, stored and handled in accordance with local policy. No additional labelling for clinical trial purposes is required.

10.5 Administration of Intervention

- WB may be administered via either the intravenous (IV) or intraosseous (IO) route, according to standard practice.
- RBC and thawed plasma may be administered via either the intravenous (IV) or intraosseous (IO) route, according to standard clinical practice.
- LyoPlas may be administered via either the intravenous (IV) or intraosseous (IO) route after reconstitution in water, in accordance with the manufacturer's instructions.

Fluid boluses should be administered according to standard practice which will usually require that they are delivered through a fluid warming device.

10.6 Administration Schedule

Each patient requiring pre-hospital blood transfusion should receive either the intervention (up to 2 units of WB) or control (up to 2 units of red blood cells and 2 units of plasma), followed by additional blood components as required.

The volume of blood product given will follow local protocol. For adult patients this would usually be up to 2 units of whole blood, or up to 2 units each of red blood cells and plasma. For children, local protocol should be followed regarding the comparable number of units that should be received.

RBC, thawed plasma (or lyophilised plasma) will be administered as per current standard of care.

10.7 Concomitant treatment

WB, RBC and LyoPlas have been prepared with citrate, therefore **solutions containing calcium must not be administered concurrently through the same cannula**. Medicinal products should not be added to WB, RBC, thawed plasma, or LyoPlas. If an acute transfusion reaction (ATR), including allergic reactions, is suspected following IV/IO infusion of either WB, RBC, thawed plasma or LyoPlas, the transfusion should be stopped immediately. The IV/IO cannula should be retained and the transfusion reaction managed as per standard clinical practice.

11. SAFETY REPORTING

The principles of ICH-GCP will be followed, which require Investigators and Sponsors to follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section.

In addition to the trial safety reporting procedures, hospital staff will be responsible for reporting all transfusion-related adverse events/reactions via Serious Hazards Of Transfusion and Serious Adverse Blood Reactions and Events (SHOT/SABRE) according to standard procedures (as required by BSQR UK 2005). Each individual transfusion laboratory issuing blood has their own their local policies and procedures for the response to a possible transfusion event and should ensure full compliance with their own licence and MHRA. Where the receiving hospital transfusion laboratory is different from the issuing hospital transfusion laboratory, then both parties should co-ordinate to ensure traceability of blood components and reporting. Regulations require that the hospital transfusion laboratory that provided the blood component(s) must be informed immediately of all adverse events and reactions. Advice on clinical management and investigation of serious adverse reactions can be obtained from the hospital consultant responsible for blood transfusion at the coordinating hospital.

11.1 Definitions

Definition of standard terms:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant who has received the trial intervention(s), including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to the trial intervention(s) which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening* • requires inpatient hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect

	Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention(s), based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the trial intervention(s) in question set out in the reference safety information***.

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

***There is only one IMP being used in this trial (LyoPlas (freeze-dried plasma). The Reference Safety Information for this IMP is section 5 of the approved SmPC. For the other trial interventions (which are blood components - WB, RBC, FFP), expectedness will be assessed against the list of known transfusion reactions (in section 11.5 of this protocol).

11.2 (Serious) Adverse Events

SWiFT trial participants have suffered traumatic injury and by definition will have multiple (serious) adverse events during their transfer to hospital and admission (related to their traumatic injury). Most of the AEs occurring in SWiFT, whether serious or not, will therefore be anticipated in the sense that they are recognised and accepted complications/consequences of major trauma.

Investigators will report **serious adverse events**, other than the exemptions which are listed in **section 11.2.1**. Non-serious adverse events will not be recorded.

All serious adverse events/reactions which relate to the administration of the pre-hospital WB, standard of care components (RBC and FFP) or LyoPlas must be reported as Serious Adverse Events.

11.2.1 Events that do not Require Reporting

The following are regarded as anticipated SAEs (i.e. are recognised complications/consequences of major trauma) and are excluded from recording and reporting:

- Death (related to trauma)
- Organ failure
- Multi-organ dysfunction syndrome
- Acute respiratory distress syndrome
- Infection (any anatomical site)
- Venous thromboembolism: deep vein thrombosis or pulmonary embolism

SAEs that are related to a pre-existing condition are not required to be reported.

11.3 Reporting Procedure – Site

11.3.1 Reporting Period

Details of all SAEs (except those which are excluded, see section 11.2.1) will be documented and reported from the date/time of commencement of the protocol defined treatment, up to 14 days post-treatment or until discharge from acute care (whichever occurs first). SAE reporting is only required during the primary hospital admission.

11.3.2 Initial Reporting

SAEs should be reported to NHSBT CTU on an SAE Form as soon as possible, and no later than 24 hours after becoming aware of the event. Each report added to the eCRF will be automatically notified to NHSBT CTU. NHSBT CTU will perform an initial check of the report and request any additional information if required. Additional and further requested information (follow-up or corrections to the original case) should also be added to eCRF using a new SAE Report Form. NHSBT CTU will ensure that all SAEs are reported to the Sponsor.

TO REPORT A SERIOUS ADVERSE EVENT:
https://nhsbt.openclinica.io

The Research Team at site will be required to respond to any related queries raised by the SWiFT Trial Team as soon as possible.

The Principal Investigator is responsible for assessing causality of events according to the criteria below. A separate causality assessment is required for each trial intervention that has been administered to the participant.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial drug or intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial drug or intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	The evidence is clearly in favour of attributing the adverse reaction to the trial drug or intervention
Definitely	There is conclusive evidence beyond reasonable doubt attributing the adverse reaction to the trial drug or intervention.

If the eCRF is unavailable for any reason, a paper version of the form should be emailed to serious_adverse_events@nhsbt.nhs.uk.

11.3.3 Follow-Up Information

Participants should be followed-up until resolution or stabilisation of the event. Follow-up information should be provided as soon as possible.

11.4 Reporting Procedure – Trial Office

On receipt of an SAE Form, seriousness and causality will be reviewed independently by the Chief Investigator (CI; or nominated delegate). An SAE judged to have a reasonable causal relationship with the trial intervention will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI "or delegate(s)". If the CI "or delegate(s)" disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report. The CI (or nominated individual) will also assess all SARs for expectedness (see section 11.5).

If the event is **related** to the study intervention(s) and **unexpected**, it will be reported to the REC within 15 days of the CI becoming aware of the event (the MHRA will also be notified if the event is related to the IMP, LyoPlas – this must happen within 7 days for any fatal/life-threatening SUSARs). All PIs will be notified if such an event occurs.

11.5 Expectedness

For events which are considered possibly, probably or definitely related to a blood component (WB, RBC, FFP) or the IMP (LyoPlas), expectedness must be assessed.

Blood Components:

Expected transfusion reactions relevant to the blood components under investigation (WB, FFP, RBC) are listed here. Refer to the SHOT website for the latest definitions (www.shotuk.org/reporting). All serious adverse reactions and adverse events related to manufactured blood products and Lyoplas should be reported on the Yellow Card scheme. (https://yellowcard.mhra.gov.uk/)

- FAHR (Febrile, allergic, and hypotensive reactions) formerly known as Acute transfusion reactions (ATR), that could result in shock or cardiac arrest.
- HTR (Haemolytic Transfusion Reactions), acute or delayed.
- PTP (Post Transfusion Purpura)
- TA-GvHD (Transfusion-associated Graft versus Host Disease)
- TACO (Transfusion-Associated Circulatory Overload)
- TAD (Transfusion-Associated Dyspnoea)
- TRALI (Transfusion-Related Acute Lung Injury)

NHSBT CTU, on behalf of the Sponsor, will undertake the expectedness assessment.

LyoPlas:

The Reference Safety Information will be section 5 (Side Effects) of the approved SmPC. NHSBT CTU, on behalf of the Sponsor, will undertake the expectedness assessment.

In cases where the nature or severity of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

11.6 Pregnancy

It is possible that pregnant patients may be included in the study if attended by participating Air Ambulance Services and if they are deemed to require pre-hospital transfusion. However, as the intervention is no different to standard care in this context no specific additional follow up of these

participants is deemed necessary. Safety monitoring of these participants will be achieved as per standard practice.

11.7 Administration of whole blood to non-trial participants in NHS hospitals

After WB has been administered to 100 trial participants and if there are no safety concerns, the product will be permitted for use in other patient groups (outside of the pre-hospital setting) to reduce blood wastage (as agreed by the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC), which includes representation from the MHRA). Once whole blood has been administered to 100 trial participants, the DMC will review the safety data and provide a report to the Standing Advisory Committee on Blood Components (SACBC) and JPAC for approval. Once approved by these Committees, hospitals who are being supplied with WB as part of the trial will then be able to issue the product to other patients who require RBC and plasma for treatment of bleeding (non-traumatic). Safety monitoring of these patients will be achieved via SHOT, as per standard practice.

12. STATISTICS AND DATA ANALYSIS

12.1 Sample size calculation

The trial will use a group sequential, superiority design and one interim analysis with O'Brien Fleming stopping boundaries, to inform early stopping for harm or benefit.

Using unpublished data from the red cell and plasma (RCP) pilot study, the composite endpoint of 24-hour mortality or massive transfusion (defined as the total blood components given ≥10 units) in the first 24 hours, was calculated as 68%. The Red Cell and Plasma study prospectively collected clinical data from all trauma patients who required pre-hospital blood transfusion from eight AAS in England between October 2018 and October 2020. The aim of this study was to compare the clinical outcomes of trauma patients who were transfused a combined blood component (red cell and plasma) in London in the pre-hospital setting versus those who received RBC and thawed plasma (or lyophilised plasma) outside London (seven AAS).

The events (mortality and transfusion requirements) had similar frequencies within the data and were also deemed to be similarly important clinically:

	Blood product transfusion ≥10 units in 24 hours	
24-hour survival	*No*	*Yes*
Alive	214 (32%)	204 (30%)
Dead	194 (29%)	61 (9%)

The two outcomes were also examined by type of injury (blunt or penetrating) and RCP vs non-RCP. RCP data was from London only. Overall, for participants experiencing a penetrating injury (32%) (which was more common in London / the RCP arm) compared to blunt injury, they had a slightly higher mortality (40% vs 37%), required more blood components (44% vs 37%) and the composite endpoint was therefore higher when compared to blunt injury (75% vs 65%). The overall percentages demonstrated in this study should be similar to those observed during the SWIFT trial hence we have used a baseline event rate of 68% in our calculations. In addition, the randomisation list will be stratified by AAS, to ensure that there is balance between the two treatment arms within each AAS.

Several studies have reported that WB transfusion versus blood components (or addition of platelets to red cells and plasma resuscitation) are likely to reduce mortality and overall transfusion, hence the reason for choosing this composite outcome:

- Williams (2019) (14) reported that a similar number of units were received in ED, although fewer units of RBC, plasma and overall products after leaving ED (overall products the median (IQR) were 0 (0-4) for WB and 3 (0-10) for traditional component therapy)
- Spinella (2009) (10) reported a 24-hour mortality rate of 4% in WB vs 12% in component therapy (67% relative difference and 8% absolute difference). A higher chance of massive transfusion in WB compared to component therapy (89% vs 78%) though differences were expected as the groups were determined by the blood products transfused.
- The PROPPR trial sub-study (20) showed an 11% absolute (66% relative difference) in 24-hour mortality between those patients who did and did not received platelets.
- Perkins 2011 (13) reported a significant reduction in blood products use at 24 hours in the WB group. The RCT of WB versus components showed similar results, but only in a sub-group analysis of patients without severe brain injury (median [IQR] 24 hour total transfusions was 11 [5,17] vs. 16 [4,41], p=0.02) (12) (13).

Hence, combining all the evidence above, we have powered the study to detect a 12% absolute (38% relative) difference in the composite endpoint between the two treatment arms (68% vs 56%).

If a patient is in traumatic cardiac arrest (TCA) on arrival of the AAS, a noticeably lower survival to hospital rate has been observed (26% in the RCP pilot study). Note in this trial a TCA patient is define using the European Resuscitation Council definition i.e. a clinical diagnosis based on agonal or absent respirations and absent central pulse (24). These participants will therefore be excluded from the main analysis of the primary outcome and will be analysed separately (please see 12.4 for details). This is also in line with recent trials in the pre-hospital setting (RePHILL trial protocol, COMBAT (16).

A two-sided test with 85% power, 5% type I error, 1-1 allocation and one interim analysis would require 602 participants. After allowing for 25% for excluding TCA participants (identified from RCP pilot study) and an additional 5% drop out, the total number of participants required for this trial is 848. The sample size calculation was conducted in SAS v7.1.

The interim analysis will be conducted after 400 participants, who did not experience TCA, have been randomised to inform early stopping of the trial in the case of strong evidence of harm or benefit.

A blinded analysis after the first 300 participants have been randomised and reached 24 hours will allow us to reassess sample size requirements and recruitment rates, including estimating the underlying the overall event rate, the rates used for dropout and proportion of cardiac arrest participants, and if necessary, modify the design of the study (25).

12.2 Internal Pilot Phase

The trial has an embedded internal pilot to assess recruitment rate and primary outcome data completion. This will be conducted nine months after the first participant has been recruited, assessing data from the first 6 months. The progress will be assessed against the target figures, as listed below:

- ≥ 130 participants have been recruited (including those that had a TCA), or
- 4 or more Air Ambulance Services are open to recruitment

- primary outcome completion rate is >80%

If the target figures have not been met, strategies will be developed and implemented to improve the rates. This may include opening additional trial sites or providing additional site support and training. The Trial Steering Committee will be actively involved in this review.

12.3 Statistical Analysis Plan

Analyses will be described in detail in a full Statistical Analysis Plan (SAP). This section summarises the main points.

12.3.1 Summary of baseline data and flow of participants

The following factors will be used to assess baseline comparability of the randomised groups:

- Age in years, reported as a median (IQR)
- Number and proportion of paediatric participants (defined as <16 years)
- Sex (male or female)
- Type of injury (blunt or penetrating)
- Nature of traumatic injury (high or low energy transfer)
- Injury Severity Score, reported as a median (IQR), defined as the sum of the squares of the highest AIS grade in each of the three most severely injured areas. Note if the participant is dead upon arrival to hospital, then the ISS is not calculated and hence will be assumed to be 75 (the maximum score). (26)
- Systolic blood pressure (mm Hg), reported as a median (IQR)
- Heart rate (per minute), reported as a median (IQR)
- Glasgow Coma Scale, reported as a median (IQR). This score measures eye opening, verbal and motor response functions (27) (28)
- Age of blood in days, reported as a median (IQR). This will be determined using routinely collected NHSBT data.

A CONSORT diagram will be produced to show the flow of participants through the trial.

12.3.2 Primary outcome analysis

The primary outcome will be determined as the proportion of participants who have either died (from all causes) or received 10 or more units of blood components, within the 24 hours from randomisation (a participant is considered randomised and entered into the trial when the trial intervention box has been opened). The following will be included in the blood component count: RBC, platelets, whole blood, thawed plasma (or Lyoplas) and cryoprecipitate. In this trial, for the purposes of analysis, two units of whole blood will be counted as equivalent to four total units due to the volume difference between the intervention and control arm, the fact that two units of whole blood contain the equivalent of two units of plasma plus two units of packed RBCs, and for the massive transfusion part of the primary analysis, both arms will start will an equal baseline (section 10.3). The composite outcome will be analysed using a mixed logistic regression model with adjustment for AAS, fitted as a random effect. A superiority hypothesis will be tested and the results from the adjusted analysis will be considered the primary analysis.

12.3.3 Secondary outcome analysis

All-cause mortality at 6 hours, 24 hours, 30 days and 90 days, the proportion of participants who receive 10 or more units of any blood components and presence of coagulopathy will each be analysed separately using the same model that is described for the primary outcome.

Organ failure free days, days in critical care and an acute care hospital will reported as a median and IQR, by treatment arm and overall.

Units of each blood component received in the 24 hours after randomisation will be summarised with a median and interquartile range and analysed using a negative binomial model, with adjustment for AAS.

Amount of millilitres (mls) of cell salvage at 24 hours after randomisation and lactate, base excess and pH level in first sample taken on arrival at acute care hospital will be analysed separately using a mixed linear regression model, with adjustment for AAS.

For each of the additional haemostatic agents, the number of participants who received each agent will be presented by trial arm and overall.

Thrombosis (arterial or venous thrombosis) up to 30 days after randomisation and transfusion reactions/events relating to pre-hospital blood components which have been reported to SHOT (Serious Hazards of Transfusion) occurring in the first 14 days after randomisation, will be summarised.

All Cost-Effectiveness outcomes will be analysed in the economic evaluation.

12.4 Additional analyses

We are interested in how the following factors are associated with the primary outcome. However, as these factors occur post randomisation and are not baseline characteristics, they cannot be subgroup analyses. Instead, each factor will be presented by treatment arm for the primary outcome. Then each factor will be separately fitted in the primary outcome model to assess if the factor is significantly associated with the primary outcome after the other risk adjustment, and how it affects the treatment effect. For the age of whole blood, only those in the intervention arm will be included and hence the data will just be tabulated by level of the factor against the primary outcome and the treatment effect will not be explored.

1. Anaesthetised prehospital or not
2. Transport time to hospital: ≤20 minutes vs > 20 minutes
3. Age of whole blood: Age of units of whole blood in days categorized into young (1-14 days) and old (>14 days)

As the number of participants expected to experience TCA is 25% (approximately 214 of our 848 participants), an additional analysis will be conducted for these participants. This will be totally separate from the main analysis and will include a table showing the number and percentage of participants who experience a TCA by trial arm and this data will be compared using a Chi-Squared test to show any differences between trial arms. In addition, the primary outcome will be replicated.

As it is anticipated that only 26% of TCA participants will survive to hospital, none of the secondary or other outcomes will be replicated for this group.

12.5 Subgroup analyses

The primary outcome analyses will be replicated for four subgroups:

1. Presence of a traumatic brain injury defined as Abbreviated Injury Scale head score 3 or above[25]
2. Adult vs paediatric
3. Blunt vs penetrating traumatic injury
4. Injury Severity Score: ≤15 vs 16-25 vs ≥26

The last two of these subgroups have been added to allow comparison to previous trials.

We anticipate:

- Higher mortality rates in those with a traumatic brain injury compared to no head injury and also those with penetrating rather than blunt trauma, though we expect the effect of whole blood to be the same in each subgroup.
- That the effect of whole blood on mortality or massive transfusion requirements will be no different for adult vs paediatric subgroups.
- For participants with an ISS of ≤15 or ≥26 only a small or no difference is expected between the two treatment arms for mortality or amount of blood components received, despite whether the participant receives whole blood or control. However, for moderately injured participants (ISS 16-25) we anticipate a lower mortality rate for those who receive whole blood.

12.6 Interim analysis and criteria for the premature termination of the trial

There will be one interim analysis which will look for harm or benefit (not futility), using the O'Brien Fleming method. This will be conducted by the trial statistician, once 400 participants have been recruited (excluding those who were found to be in TCA upon arrival of the Air Ambulance Service clinical team). In addition, the dropout and TCA rate will be examined to ensure that they are in line with the expected 5% and 25% respectively, which was initially anticipated.

This analysis will be presented to and reviewed by the DMC only and will help inform early stopping of the trial in the case of strong evidence of harm or benefit. The stopping rules will be used as a guideline, alongside the other safety data available to the DMC, and used as part of their overall assessment of the trial. They will have overall oversight and can recommend terminating the trial early for these or any other safety concerns. The TSC will have the ultimate authority to stop or modify the trial.

The DMC members will be the only individuals, along with the trial statisticians, to see outcome data by arm and overall while the trial is ongoing.

In addition, the blinded sample size reassessment may lead to premature termination of the trial. This could occur if for example, the estimates observed are significantly different from those anticipated in the original sample size calculations and hence this significantly increases the total sample size. The outcome of this assessment will be reviewed by the DMC and trial statisticians only and a recommendation will be sent to the TSC and TMG.

12.7 Participant population

All analyses will be performed on a modified intention to treat basis, to exclude participants who experience a traumatic cardiac arrest, but will include all other randomised patients on whom a value of the response variable has been obtained, including those randomised in error and regardless of the participants' adherence to the protocol. The data will be presented and analysed according to the arm to which the participant was randomised, regardless of whether they received the randomised intervention or not.

The primary outcome (and none of the secondary outcomes) will be replicated per protocol which will exclude participants who experience a traumatic cardiac arrest, those who experience a protocol deviation, were randomised in error or were withdrawn from the trial. The data will be presented and analysed according to the arm to which the participant was randomised.

12.8 Procedure(s) to account for missing or spurious data

For the primary analysis, any missing data for the primary and secondary outcome measures will be treated as missing data and not be imputed. If an outcome has data missing for more than 25% of participants, then the analysis will not be undertaken. All missing primary and secondary outcome data will be summarised.

A sensitivity analysis will be conducted if the primary outcome is missing for more than 5% of participants, which will impute the composite endpoint.

12.9 Other statistical considerations

All analysis will be two sided and p-values of less than 0.05 will be considered as statistically significant.

Protocol deviations will be monitored throughout the trial by the TMG, DMC and TSC, and will be assessed as minor or major and whether they influence the statistical analysis.

13. ECONOMIC EVALUATION

The economic evaluation will establish the resources required to provide the whole blood intervention, estimate intervention and standard care costs, and conduct a full incremental cost-effectiveness analysis (CEA). The intervention costing and CEA, based on within-trial data, will be undertaken against a primary perspective of the NHS/Social Care.

Cost and outcome data will be synthesised to present incremental cost-effectiveness ratios for: i) the primary outcome, to give cost per death averted/participant received a total of 10 or more units of any blood components in the first 24 hours following randomisation and; ii) the policy relevant economic endpoint - cost per quality-adjusted life-year (QALY) at 3 months post-randomisation.

Key areas of intervention resource use will be identified, measured (e.g. whole blood production resources such as specific filters/bags, blood product wastage, clinical time), and costed to estimate the cost-per-participant of the intervention. This process will also be undertaken for standard care.

Participant hospital resource use will be captured up to discharge from hospital by research nurses, and subsequent health, social and wider care service use will be captured from participants at 3 month follow-up. A self-report resource use questionnaire will be developed in collaboration with the patient involvement group for the trial and the Trial Management Group, informed by the core items for a standardised resource use measure (29) and the Database of Instruments for Resource Use Measurement (DIRUM) (30). Nationally-recognised health/social care unit costs will be applied to the resource use data (31) (32).

The EQ-5D-5L (33) (34) will be used with the UK health state value set recommended by the National Institute for Health and Care Excellence at the time of data analysis (35) (36) to estimate quality-adjusted life years (QALYs). Incremental costs and incremental QALYs over 3 months will be used to estimate the cost-per-QALY of whole blood versus standard care.

The internationally-recognised CHEERs guidelines for reporting cost-effectiveness studies will be followed (37). Planned analyses will be described in a full Health Economics Analysis Plan. Descriptive statistics will be used to summarise the costs (by type of service) and QALYs. Regression analyses will be used to adjust for systematic differences between intervention and control arms that have not been accounted for by randomisation, and bootstrapping will be employed. Cost-effectiveness acceptability curves will be presented (38) and multiple imputation will be used as appropriate to correct for bias that may result from data that is missing at random (93). Analyses will also explore uncertainty, and provide a clear, policy-relevant presentation of findings.

14. QUALITATIVE RESEARCH

Alongside the SWiFT trial, a sub-study will be conducted to assess the acceptability and implementation of the intervention (whole blood). In this sub-study, qualitative methods will be used, involving interviews and focus groups with operational staff, patient representatives and blood donors. The objectives of the sub-study are to:

- Gain a deeper understanding of the contexts within which the intervention will be delivered and its impact on local (hospitals) and central (central blood service) processes and systems.
- Identify implementation mechanisms and factors that might promote and inhibit the incorporation of the intervention into standard care.
- Identify factors that influence the acceptability of the intervention from the perspective of healthcare professionals involved in the whole WB pathway (from donor to recipients).
- Inform future adoption and implementation of the WB pathway in other settings by identifying potential strategies for sustainable implementation.

Full detail on this work is covered in the **SWiFT Implementation Study Protocol**.

15. DATA MANAGEMENT

15.1 Data Collection and Source Data

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic

negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Source documents in this trial include:

- "Pre-Hospital" Case Report Form
- Informed consent forms
- Hospital records (paper and electronic)
- Laboratory test results
- Completed participant questionnaires (paper and electronic (entered directly onto the eCRF))

15.2 Data Handling

The Principal Investigator has overall responsibility for data collection at site. Participant data will be entered onto the trial database, which was designed and administered by the NHSBT CTU Data Management team using OpenClinica. The OpenClinica database will be used for electronic data capture (EDC) management and reporting on this trial. Training and instructions for completion of eCRFs will be given to each site during at site activation.

All case report forms will be electronic. Sites will be granted access to the EDC system following approval of all site registration documentation and completion of training, provided by NHSBT CTU. The eCRFs must be completed directly onto the EDC system (i.e. the database).

The NHSBT CTU staff will be in regular contact with local site personnel to check on progress and to help with any queries that may arise. Incoming electronic forms will be checked for completeness, consistency, timelines and compliance with the protocol.

Data related to the Implementation Study (Section 14) will be held securely on servers at Imperial College London, with access restricted only to researchers working on the project.

15.3 Access to Data

Direct access to eCRF data will be granted to authorised representatives from the Sponsor, NHSBT CTU, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.

Data related to the Implementation Study (Section 14) will be held separately, by researchers at Imperial College London. Identifiable information (e.g. names and contact details of health care professionals and patient representatives who agree to take part in the qualitative interviews and focus groups) will not be shared with other Parties. Once these details are no longer needed they will be deleted/destroyed. Recordings and transcripts will be pseudo-anonymised.

15.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. All essential documents will be archived for at least 15 years or in accordance with national law, whichever is longer after completion of trial. Destruction of essential documents will require authorisation from the Sponsor. The Sponsor will be responsible for archiving the TMF.

The sites will be responsible for archiving the Investigator Site Files. The sites must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g. locked filing cabinets in a room with restricted access). All data must be accessible to the Sponsor with suitable notice for inspection. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by the Sponsor.

Following completion of analysis, the trial database will be archived in accordance with the Trial Sponsor policies.

16. MONITORING, AUDIT & INSPECTION

The frequency, type and intensity for routine monitoring and the requirements for "for cause" monitoring will be detailed in a separate monitoring plan.

In addition to potential GCP inspections or audits by the host R&D department, the Sponsor and NHSBT CTU reserve the right to conduct site audits, either as part of its on-going audit programme, or in response to adverse observations.

17. ANCILLARY STUDIES

SWiFT participants will be eligible for enrolment in the ACIT-ED study (IRAS: 71328), at sites which are participating in this study. ACIT-ED will specifically help to understand the treatment effect of whole blood transfusion after injury through a single blood sample taken on admission – data collected as part of the SWiFT trial will be shared with ACIT-ED (once a Data Sharing Agreement has been put in place). No patient identifiable information will be shared.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Research Ethics Committee (REC) Review & Reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent form and other relevant documents.
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. If necessary, an amendment will also be reviewed and approved by the NHS R&D departments before implementation.
- All correspondence with the REC will be retained in the Trial Master File (TMF).
- An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial has ended.
- It will be the responsibility of the CIs or delegate to produce the annual reports as required.
- The NHSBT CTU on behalf of the CIs will notify the REC of the End of Trial.
- Within one year of the end of the trial, the NHSBT CTU on behalf of the CIs will submit a final report with the results, including any publications/abstracts, to the REC.

18.2 Peer review

The research proposal this protocol has been based on has been independently peer reviewed by three independent experts, based both within and outside of the UK. The peer review process was initiated by the trial Sponsor.

18.3 Public and Patient Involvement

Patient involvement has been sought through NHSBT's Patient and Public Advisory Group (PPAG). A panel of members were convened to review the trial proposal and patient information documents.

In addition to this, there are two lay representatives on the Trial Steering Committee, who will provide their input at all stages of the trial.

18.4 Regulatory Compliance

The trial will not commence until the following approvals are obtained: Clinical Trial Authorisation (CTA) from the MHRA, a favourable opinion from the REC and HRA approval. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the study, the Chief Investigators/Principal Investigators or designees will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigators or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

18.5 Protocol compliance

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, for example it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.
- Accidental protocol deviations can happen at any time and must be reported to the Trial Manager.
- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

18.6 Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

The site will inform NHSBT CTU as soon as they are aware of a potential serious breach, so NHSBT CTU can report the breach to the trial Sponsor. The NHSBT CTU and the Sponsor will discuss the breach and decide whether the breach is classified as serious. If the breach is serious, NHSBT CTU will report to the REC and MHRA within 7 days of becoming aware of the breach as per the UK regulatory requirements.

NHSBT CTU will notify the REC and MHRA in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

18.7 Data Protection and Patient Confidentiality

All investigators and trial site staff must comply with the requirements of the UK Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the regulations' core principles. The confidentiality standards will be maintained by coding each patient enrolled in the trial through assignment of a unique participant identification number. Only pseudo-anonymous data will be entered into the trial database.

Limited patient identifiable data points will be required, to enable linkage to the TARN/ICNARC datasets (described in section 9.7). Consent will be obtained via the participant/their legal representative/Parent/Guardian to collect these data items. If informed consent cannot be obtained (e.g. for a participant who has died before admission to hospital), we will collect this data under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group). Identifiable information will be held separately from the trial database and will not be retained for the analysis.

The required data will be transferred directly to NHSBT CTU via the nhs.net secure network. It will be stored on NHSBT servers with access limited only to the trial statistician(s) and data manager(s). The trial statistician(s) will ensure that onward data transfer (to TARN/ICNARC) is performed securely and in agreement with the terms of the relevant Data Transfer Agreement.

Consent will be sought from participants to inform their General Practitioner (GP) of their enrolment in the trial.

Data generated by this trial must be available for inspection upon request by representatives of MHRA and other national and local health authorities, NHSBT CTU monitors, representatives and the REC for each trial site, as appropriate. The data controller for this study is NHSBT.

18.8 Financial and Other Competing Interests

At the time of writing the protocol, the Chief Investigators, Principal Investigators and all members of the trial committees had no competing interests that might influence trial design, conduct or reporting.

Any potential disclosures arising during the trial will be notified to the Chief Investigators. These will include ownership interests that may be related to products, services or interventions that may be significantly affected by the trial, commercial ties (including pharmaceutical and/or technology company, or behaviour modification) and any non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).

18.9 Indemnity

SWiFT is an NHS sponsored research trial; therefore, the NHS indemnity scheme applies to this trial when it is being conducted in the UK. In the case of negligent harm, health care professionals undertaking clinical trials or studies on volunteers, whether healthy or patients, during their NHS employment are covered by NHS Indemnity.

Insurance for Clinical Trials sponsored and managed by NHSBT is covered by the NHS Resolution Schemes as follows:

- The Clinical Negligence Scheme for Trusts (CNST): for negligent harm and also product liability. Any clinical negligence liabilities owed to a patient/participant arising out of or in connection with practical implementation of clinical trials sponsored by NHSBT are covered by the Scheme.
- The Liabilities for Third Parties Scheme (LTPS): covers employers' and public liability claims from NHS staff, patients and members of the public. These range from straightforward slips and trips to serious workplace manual handling, bullying and stress claims. LTPS covers claims arising from breaches of the Human Rights Act, the Data Protection Act and the Defective Premises Act, as well as defamation, unlawful detention and professional negligence claims.

Cover is also provided by:
The Department of Health Contingent Liability Minute: for non-negligent harm including trial design and no-fault compensation https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/10894/nhsbt-and-doh-framework-agreement-2014.pdf (Clause 10.6). Non-negligent or no-fault compensation is an arrangement to pay compensation for harm where no legal liability arises or is admitted for any person (i.e. a participant has suffered harm as a result of taking part in the research but there is no negligence in its management, design or conduct and no other liability arises such as product liability).

18.10 Access to the Final Trial Dataset

The final data set will reside with NHSBT. The Chief Investigators will have access and can approve exceptional access for other members of the trial team to facilitate analysis or to cover for absences. Access to the final data set for additional analyses will be permitted under the agreement of the trial review committee and according to the trial publication policy (see section 19 below).

19. DISSEMINATION POLICY

19.1 Dissemination Policy

- Ownership of the data arising from this trial reside with the Sponsor. On completion of the trial the data will be analysed and tabulated, and a final trial report prepared. The manuscript will be prepared by the relevant members of the writing group and the SWiFT Trial Management Group.
- Draft copies of all trial manuscripts will be circulated to all collaborators for review prior to their submission for publication. Responsibility for all trial publications will rest with the TMG.

- The main trial results will be presented at national and international conferences and published in a peer-reviewed journal, on behalf of all collaborators. All presentations and publications related to the trial must be authorised by the TMG.
- The members of the TSC and DMC will be listed with their affiliations in the acknowledgements of the main publication. The funders will be acknowledged within all publications.
- The final report's abstract and reference will be accessible on the SWiFT trial website.
- Participants will be able to access the results through the SWiFT trial website.
- A trial identifier will be included on all presentations and publications (e.g. the ISCRTN).
- No data may be made public before publication and without agreement from the CIs and Sponsor.
- The datasets generated during and/or analysed during the trial will be available upon request from the NHSBT Clinical Trials Unit after de-identification (text, tables, figures and appendices) 9 months after publication and ending 5 years following article publication. Data will be shared with investigators whose use of the data has been assessed and approved by the trial review committee as a methodologically sound proposal.

19.2 Authorship Eligibility Guidelines

Authorship on any publications arising from this study will follow the rules laid out by the International Committee of Medical Journal Editors definitions of Authors and Contributors.

20. PROTOCOL AMENDMENTS

Amendment Number	Protocol Version	Date	Author(s) of changes	Details of changes made
n/a	1.1	03/05/2022	Trial Management Group	Changes made at the request of the Research Ethics Committee and Confidentiality Advisory Group to the original HRA application.

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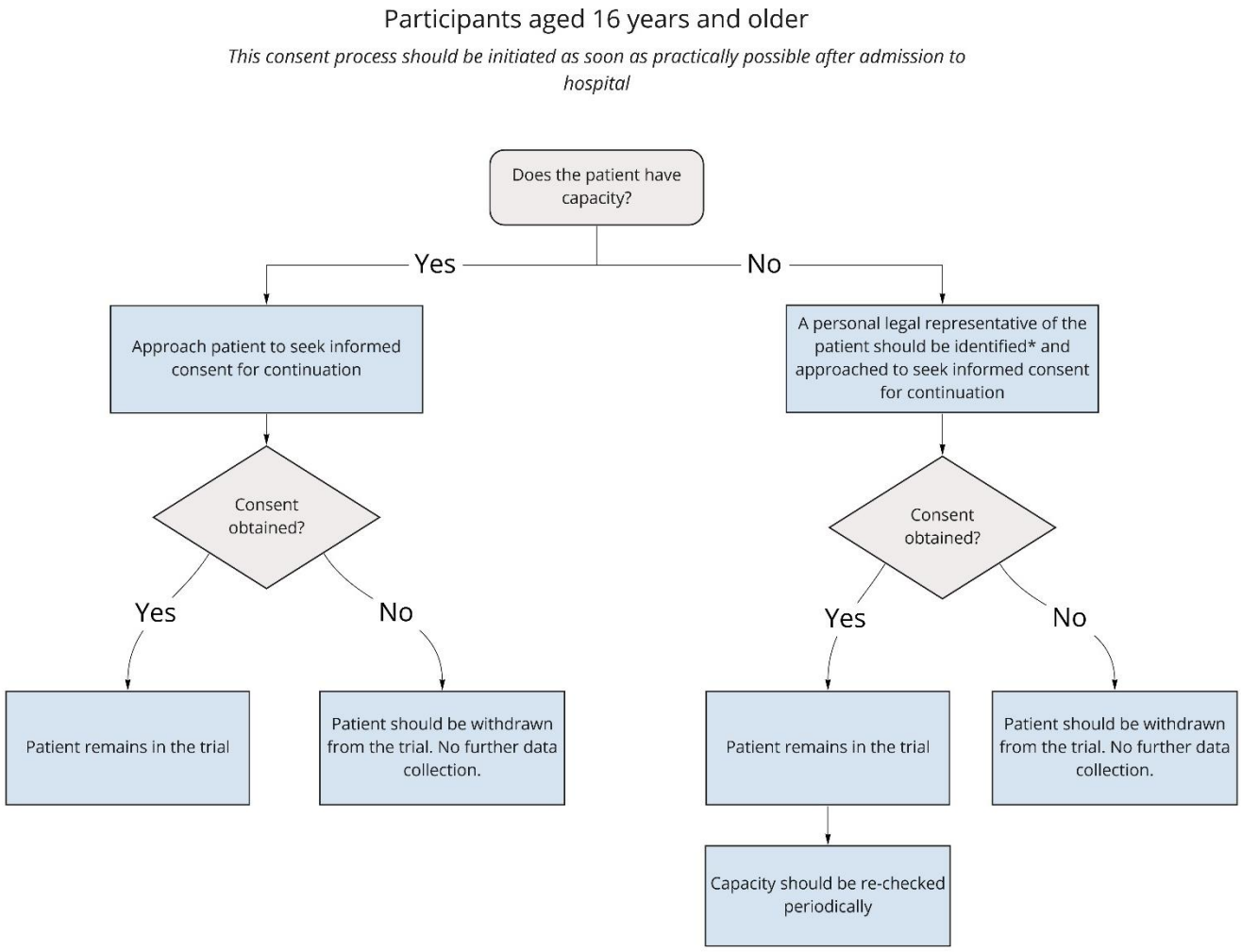
22. Appendices

APPENDIX 1 – Air Ambulance Charity Funding

The following Air Ambulances have kindly provided funding for the SWiFT trial:

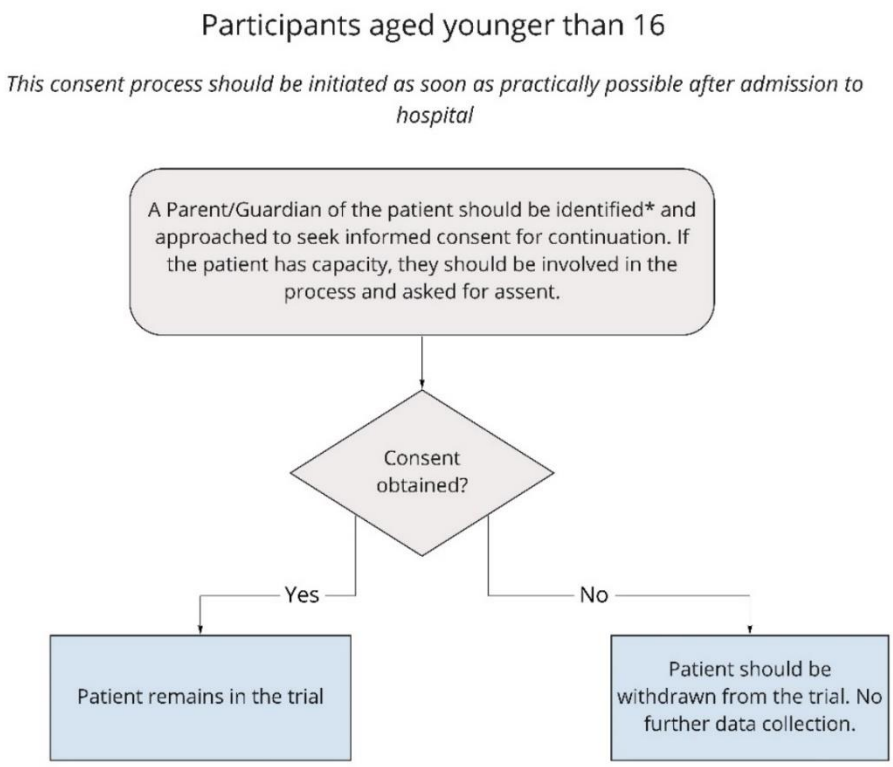
- Air Ambulance Kent Surrey Sussex (AAKSS)
- Dorset and Somerset Air Ambulance (DSAA)
- Essex and Herts Air Ambulance (EHAAT)
- Hampshire and Isle of Wight Air Ambulance (HIOWAA)
- Great North Air Ambulance (GNAAS)
- Great Western Air Ambulance (GWAAC)
- London's Air Ambulance (LAA)
- Magpas Air Ambulance (Magpas)
- North West Air Ambulance (NWAA)
- Thames Valley Air Ambulance (TVAA)

APPENDIX 2 – Consent Summary (participants aged ≥ 16 years)



*If no personal legal representative can be identified, a professional legal representative should be used instead

APPENDIX 3 – Consent Summary (participants aged < 16 years)



*If no Parent/Guardian can be contacted, a personal legal representative should be used instead. If no personal legal representative can be identified, a professional legal representative should be used instead