A Multi-Centre Randomised Controlled Trial of Pre-Hospital Blood Product Administration versus Standard Care for Traumatic Haemorrhage

PROTOCOL

Version 2.0, 16th January 2017

Sponsor:	**University Hospitals Birmingham NHS Foundation Trust**
Chief Investigator:	**Prof. Gavin Perkins**
Co-Chief Investigator:	**Dr. Nicholas Crombie**
Coordinating Centre:	**Birmingham Clinical Trials Unit**
Funder:	**National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme**
EudraCT No.:	**2015-001401-13**
ISRCTN:	**62326938**
REC Ref. No.:	**15/SC/0691**

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

Surgical Reconstruction and Microbiology Research Centre

NHS National Institute for Health Research

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA1	18 Jul 2016	1.1	Substantial	• Update to CI • Addition of/ change to PIs • Addition/ removal of sites
SA2	22 Sep 2017	1.1	Substantial	• Addition of participating site
SA3		2.0	Substantial	• Administrative updates to TMG (formal change to CI requested as part of SA1) • Updates to members of the oversight committees • Clarification on the primary outcome • Update to exclusion criteria • Update to include delivery of interventions by the intraosseous route • Clarification of the informed consent process • Clarification on the randomisation and enrolment process • Update to the schedule of events • Clarification of AE reporting • Clarification on data collection • Statistical updates • Clarification on monitoring requirements • Addition/ removal of participating sites • Personnel changes at site (PI)

Trial Management Group

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Participating Sites
Intervention Delivery Sites (IDS): *responsible for treating patients on scene and delivering the trial intervention prior to hospital admission.*
• West Midlands Ambulance Service NHS Foundation Trust (Midlands Air Ambulance/ MERIT) • The Air Ambulance Service (TAAS) • MAGPAS • East Anglian Air Ambulance • Essex & Herts Air Ambulance
Receiving Hospital Sites (RHS): *secondary care sites where patients will be admitted to following trial treatment.*
• University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital • University Hospitals Coventry and Warwickshire NHS Trust, University Hospital • University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital • North Bristol NHS Foundation Trust, Southmead Hospital • Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital • Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital • Norfolk & Norwich University Hospitals NHS Foundation Trust, Norfolk And Norwich University Hospital • Nottingham University Hospitals NHS Trust, Queen's Medical Centre

RePHILL Trial Office

For general protocol related queries and supply of trial materials:

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Intervention Box Allocation

Telephone: 0800 953 0274

Database: https://www.trials.bham.ac.uk/RePHILL/

Participant Enrolment

Database: https://www.trials.bham.ac.uk/RePHILL/

Safety Reporting

Fax SAE Forms to: 0121 415 9135 or 0121 415 9136

Chief Investigator and Sponsor Signatures

The Chief Investigator and Sponsor have discussed this protocol and agree to abide by this protocol and to conduct the trial in compliance with EU Good Clinical Practice (GCP), the applicable UK Statutory Instruments, which include the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the UK Data Protection Act (1998), the Trust Information Governance Policy (or local equivalent) and the Research Governance Framework for Health and Social Care (2005 2nd Edition; as amended).

Chief Investigator

Prof. Gavin Perkins

Signature Date

Sponsor Representative

Dr Chris Counsell

Signature Date

Principal Investigator Signature Page

Principal Investigator:

I have read and agree to the protocol, as described in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the Trial Steering Committee (TSC) prior to seeking approval from the Research Ethics Committee (REC).

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki and the trial protocol and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial.

Principal investigator

<insert name>

_____

Signature Date

Name of Institution

<insert name>

_____

The Principal Investigator should sign this page and return a copy to the RePHILL Trial Office

Abbreviations

AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
ASR	Acute Safety Report
ATR	Annual Transfusion Reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRPD	Clinical Practice Research Datalink
CTA	Clinical Trial Authorisation
DAT	Direct Antigen Test
DIBD	Developmental International Birth Date
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
ED	Emergency Department
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HSCIC	Health & Social Care Information Centre
HR	Haemostatic Resuscitation
ICF	Informed Consent Form
IDS	Intervention Delivery Site
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IO	Intraosseous
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
kPa	KiloPascals

MCMC	Marcov chain Monte Carlo
MHRA	Medicines and Healthcare Products Regulatory Authority
NIHR	National Institute for Health Research
NIRS	Near-Infra-Red Spectroscopy
NHSBT	NHS Blood & Transplant
ONS	Office of National Statistics
PEEP	Positive End Expiratory Pressure
PRBC	Packed Red Blood Cells
PHBP	Pre-Hospital Blood Products
PHEM Team	Pre-Hospital Emergency Medical Team
PI	Principal Investigator – the local lead investigator for the **RePHILL** Trial
PIS	Participant Information Sheet
PT	Prothrombin Time
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RHS	Receiving Hospital Site
ROTEM®	Rotational Thromboelastometry
SABRE	Serious Adverse Blood Reactions and Events
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SHOT	Serious Hazards of Transfusion
SOFA score	Sequential Organ Failure Assessment score
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SRMRC	Surgical Reconstruction and Microbiology Research Centre
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIC	Trauma Induced Coagulopathy
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
U&Es	Urea and Electrolytes
vCJD	variant Creutzfeldt-Jakob Disease

1. Trial Summary

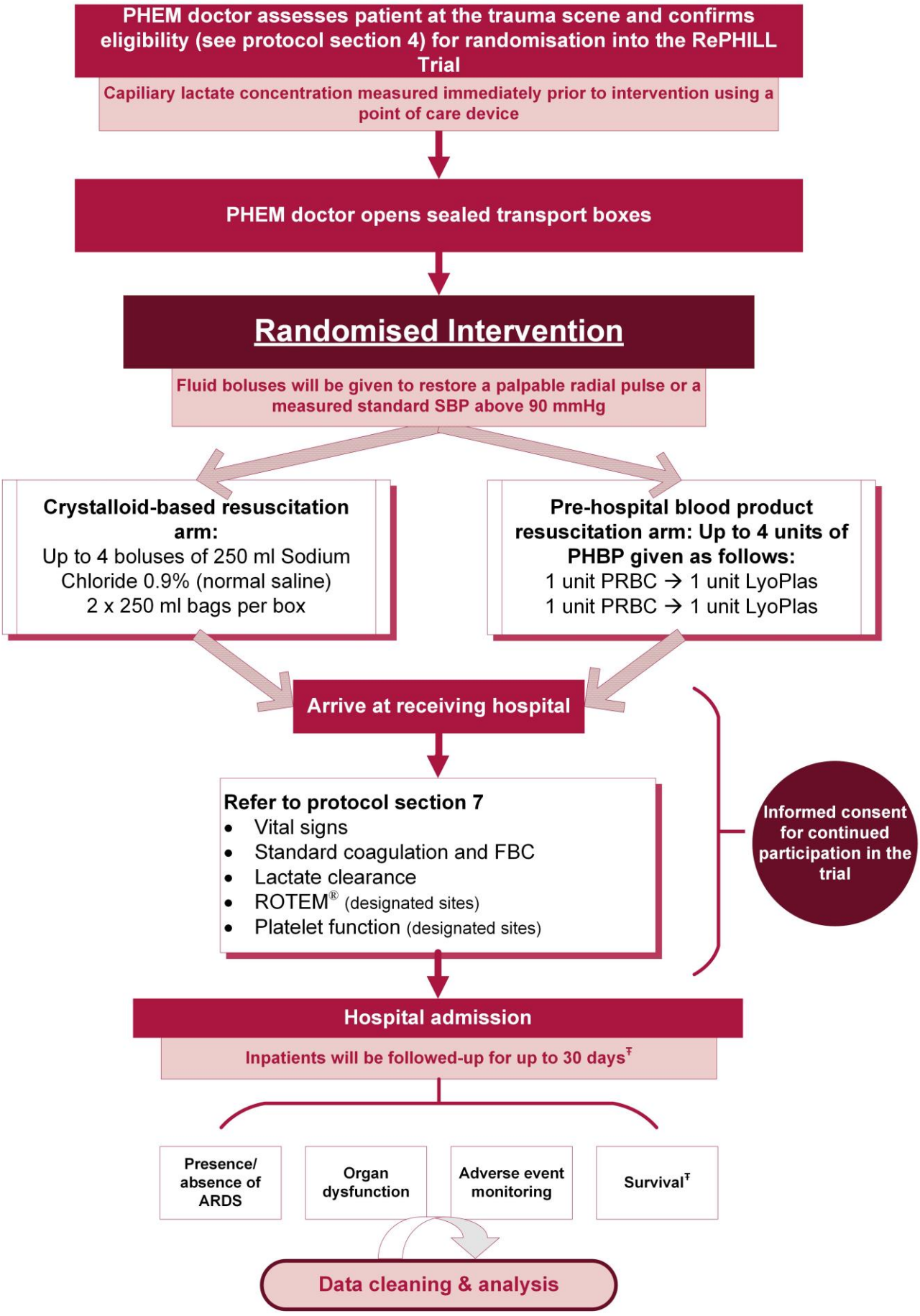
Title	**A Multi-Centre Randomised Controlled Trial of Pre-Hospital Blood Product Administration versus Standard Care for Traumatic Haemorrhage**
Acronym	**RePHILL**
Trial Design	A multicentre randomised controlled, open-label, parallel group two arm trial with internal pilot.
Aim	This trial will test the hypothesis that Pre-Hospital Blood Products (PHBP) resuscitation with up to two units each of packed red blood cells (PRBC) and lyophilised (freeze-dried) plasma (LyoPlas N-w which will be referred to as LyoPlas) will improve tissue perfusion (as measured by lactate clearance) and reduce mortality in trauma patients with haemorrhagic shock compared to the current standard practice of crystalloid resuscitation. The trial includes an internal pilot phase (25 patients) which will test logistical aspects of the trial and assess feasibility and recruitment.
Total number participants	490 (inclusive of pilot phase)
Planned trial sites	IDS and RHS.
Main inclusion and exclusion criteria	**Inclusion criteria:** • Traumatic injury • Pre-Hospital Emergency Medical team attend • Hypotension (Systolic Blood Pressure <90mmHg or absence of palpable radial pulse) believed to be due to traumatic haemorrhage. **Exclusion Criteria:** • Children (known or apparently aged <16 years) • Blood administered on-scene, prior to randomisation • Refusal of blood product administration (e.g. known Jehovah's Witness) • Pregnancy (known or apparent) • Isolated head injury without evidence of external haemorrhage • Known prisoners in the custody of HM Prison or Probation services

Outcome measures	**Primary outcome:** Composite measure consisting of: • Episode mortality[I] • Lactate clearance. A failure to achieve lactate clearance ≥ 20% per hour in the first 2 hours from randomisation[II] **Secondary outcomes:** • Individual components of the primary outcome • All-cause mortality within 3 hours of randomisation • Pre-hospital time and type and volume of fluid • Vital signs (systolic blood pressure, heart rate, capillary oxygen saturation) • (Venous) lactate concentration • Trauma-induced coagulopathy (defined as International Normalised Ratio (INR) >1.5) • Coagulation measured viscoelastically by rotational thromboelastometry (ROTEM®)[III] • Platelet function using multiple electrode impedence aggregometery (MultiPlate)[III] • Total blood product receipt • Acute respiratory distress syndrome • Transfusion-related complications • Organ failure-free day
Trial duration per participant	Main trial data collection ends at withdrawal, acute care discharge, death or at 30 days follow-up, whichever occurs first. Apart from episode mortality data which will be collected up to discharge from the acute care setting, which may be >30 days.

[I] Episode mortality refers to mortality between time of injury/ recruitment and up to discharge from the primary receiving facility to non-acute care, i.e. discharge home or to long-term care, to rehabilitation or repatriation to a hospital closer to their normal residence

[II] A patient is considered randomised and entered into the trial when the first intervention box has been opened.

[III] Selected RHS only



∓ Episode mortality data will be collected up to discharge from the acute care setting which may be >30 days

2. Background and Rationale

2.1 Existing Research and Current Practice

The administration of high ratios of plasma to packed red blood cells (PRBC) has been widely adopted for in-hospital treatment of major traumatic haemorrhage. The rationale is to provide "haemostatic resuscitation" (HR) to address trauma induced coagulopathy (TIC), which carries a fourfold increase in mortality. Evidence for HR is almost exclusively derived from observational studies. A recent Cochrane review identified no randomised controlled trials (RCTs) of plasma-based trauma resuscitation[1], while a previous systematic review found only one outdated blood component RCT of platelets[2]. The recently published Pragmatic Randomized Optimal Platelet and Plasma Ratios trial found no difference in mortality between two transfusion ratio regimens[3], both of which would be considered "haemostatic resuscitation" when compared to conventional approaches.

The only adequately performed RCT of pre-hospital fluids found that aggressive crystalloid administration increased mortality and morbidity after penetrating trauma[4]. Underlying mechanisms are believed to include increased blood pressure "blowing-off" immature clot, leading to re-bleeding. Consequently, restricted fluid regimes became standard pre-hospital care. A separate attempt to examine pre-hospital intravenous (IV) fluid resuscitation in trauma was inconclusive, with over half of the participants receiving the wrong intervention[5].

Acceptance of in-hospital HR saw the British military implement it for battlefield casualty retrieval [6]. Initially two units cells PRBC and two units of thawed plasma were carried, later increasing to four units of each. Civilian pre-hospital retrieval services have adopted a limited version of this practice, carrying PRBC alone for trauma resuscitation[7-10]. This increases demand for universal donor red cells in the absence of robust supporting evidence. Although intuitively blood product replacement should be beneficial to trauma patients, similarly logical interventions for bleeding such as recombinant activated Factor VII[11] and pneumatic anti-shock garments[12] have failed to demonstrate benefit when formally tested in randomised trials.

Implementation of the British military version of pre-hospital HR has not been possible in the UK due to logistic constraints. Thawed plasma is unsuitable for UK civilian practice due to its limited post-thaw shelf-life (24 hours) and the rarity of exsanguinating trauma, which would lead to significant product wastage. The 15 month shelf-life of LyoPlas makes it an attractive alternative, but it has not to date been tested in an RCT.

The Prehospital Air Medical Plasma (PAMPer) study (a four-year RCT which started in 2014 in the USA)[13] compares two units of thawed plasma against conventional care. PAMPer will not assess coagulopathy, nor provide information about the role of packed red cells. **RePHILL** will address

both of these in a different trauma population - one dominated by blunt mechanisms with a far lower incidence of gunshot wounds.

2.2 Clinical Studies

Meta-analysis of observational studies of in-hospital HR suggests increased survival[14, 15]. However, the minimal pre-hospital evidence is inconsistent. Consultant-delivered battlefield casualty retrieval (with access to pre-hospital blood products (PHBP) including thawed plasma) was associated with reduced mortality in major, but sub-catastrophic injuries (Injury Severity Score between 16 and 50)[16]. However, only 32% of such patients received PHBP, while 41% received advanced airway interventions, 25% received chest decompression and 60% and 46% received IV or interosseous access respectively. The study could not determine the cause of the improved survival.

A matched cohort study of casualties with similar injuries before and after the introduction of PHBP found that PHBP-recipients had 8% mortality vs. 20% in non-recipients[17]. However, pre-hospital times were longer prior to introduction of PHBP, non-recipients had greater physiological derangement and more than 50% of non-recipients received no blood products after hospital arrival, compared to median transfusions of 2 units each of red blood cells and plasma amongst PHBP-recipients. The “PHBP era” coincided with increasingly liberal in-hospital transfusions[18] and many clinicians deployed during the PHBP period had experience gained from previous deployments before PHBP were available. The only prospective cohort study to date is less favourable. Transport by civilian air ambulance with PHBP was associated with reduced 6-hour mortality compared to patients transported by an air ambulance without PHBP. Overall mortality was similar[8]. An older civilian study reported that in-flight blood receipt was associated with greater acidosis at hospital arrival than crystalloid resuscitation, but was confounded by much longer flight times in the blood recipients[19], while a recently completed case-control study of 1047 battlefield casualties found no reduction in coagulopathy or mortality from PHBP even after multivariate regression[20]. The most persuasive evidence in favour of PHBP is a retrospective study in which 50/1415 (3.5%) of blunt trauma patients received pre-hospital PRBC, with a 64% reduction in hazard ratio of 30-day mortality[21]. However, 48% of PRBC recipients were interfacility transfers rather than primary retrievals from scene (vs. 4% of non-recipients), thus survivorship bias may have influenced the results. Absolute mortality was higher amongst PHBP recipients in both the overall study and matched subgroup analysis (Brown, J., pers. comm, 08 June 2015). Our recently completed systematic review found no “moderate” or “good” quality evidence supporting PHBP resuscitation, and meta-analysis of the limited (and entirely observational) data showed no evidence of a long-term survival benefit[22].

2.3 Trial Rationale

With the increasing adoption of PHBP resuscitation for trauma in both the UK and abroad, in both military and civilian settings, it is important to determine whether this intervention is, in fact, effective. The logistical and financial resources required for the provision of PHBP resuscitation are significant and require dedicated use of valuable universal donor blood components. This trial is an opportunity to establish a robust evidence base for PHBP resuscitation; an opportunity which may fade if the trend for PHBP continues to the point that equipoise is lost despite a lack of high quality evidence, as is the case for in-hospital HR.

2.4 Risks and Benefits

The risks to participants in this trial are considered to be minimal. PHBP resuscitation delivers an equivalent intervention to participants which they would inevitably have received on arrival in hospital. The same single donor derived LyoPlas which will be used in this trial is established in the German and Israeli Defence Forces Medical Corps[23], while 10-donor mini-pool derived LyoPlas is used by the French military[24] with no reports of significant adverse events[25], though this product is not commercially available. LyoPlas N-w is produced by a quarantined single donor process – plasma is only processed if a donor has unremarkable infectivity testing at least four months after the donation was received. Plasma is then filtered, rendering it virtually cell-free. To minimise risk of transfusion-related acute lung injury, LyoPlas is only produced from leucocyte-antibody negative plasma. Transmission of prion disease (variant Creutzfeldt-Jakob Disease; vCJD) is not considered a hazard of this study – as of June 2014, no cases of vCJD have been reported in Germany[26]. Although German plasma does not meet full vCJD risk criteria for NHS Blood & Transplant (NHSBT) importation under all modelling conditions, the worst-case scenario is that if all fresh frozen plasma (FFP) requirements for patients born after 01 Jan 1996 were met from German sources, 0.1 clinical cases would result (1.9 log reduction compared to UK sourced plasma)[27]. As the majority of the approximately 245 plasma recipients in this study will have been born prior to 1996 (and would receive UK-sourced plasma in routine clinical practice), the additional risk of vCJD transmission from LyoPlas N-w use is considered to approach zero.

In contrast, massive traumatic haemorrhage leading to profound hypotension (systolic blood pressure (SBP) <90mmHg) is associated with 23% mortality[28, 29]. Any benefit from PHBP is potentially lifesaving.

2.5 Assessment and Management of Risk

The assessment and management of risk is detailed in the separate **RePHILL** Risk Assessment document. An on-going evaluation of risk will continue throughout the trial.

3. Trial Objectives and Outcome Measures

3.1 Trial Objectives

3.1.1 Principle Objective

The principle objective of this trial is to investigate the clinical effectiveness of PHBP resuscitation compared to the current standard care of restricted crystalloid based resuscitation in participants suffering from major traumatic haemorrhage.

3.1.2 Secondary Objectives

To test the hypotheses that, when compared to standard care, does PHBP resuscitation:

I. Improve blood pressure, heart rate and capillary oxygenation on ED arrival?

II. Prolong on-scene time?

III. Reduce pre-hospital fluid requirements?

IV. Reduce in-hospital transfusion requirements?

V. Reduce trauma-induced coagulopathy?

VI. Preserve platelet function?

VII. Lead to a greater incidence of transfusion-related complications, particularly acute respiratory distress syndrome?

VIII. Lead to blood product wastage?

3.2 Internal Pilot Trial

The first 6 months of the **RePHILL** trial will constitute an internal pilot to assess and confirm the trial logistics to determine if it is both feasible and practical to carry on and recruit into the trial. The pilot will be run at multiple sites to validate the multi-centre aspects of the trial.

At the end of the pilot phase, the following targets should be met to justify progression to the main trial:

- Minimum of 25 participants recruited across at least two active sites;
- In participants recruited to the trial intervention arm, at least one unit of PRBC and one unit of LyoPlas delivered to at least 80% of participants before reaching hospital
- At least 90% complete data capture
- Data Monitoring and Ethics Committee (DMEC) reports no safety concerns which would prohibit continuation to main trial.

3.3 Outcome Measures

3.3.1 Primary Outcome

The primary outcome is a composite measure consisting of:

- Episode mortality[IV]
- Lactate clearance. A failure to achieve lactate clearance ≥ 20% per hour in the first 2 hours after randomisation[V]

3.3.2 Secondary Outcomes

- Individual components of the primary outcome
- All-cause mortality within 3 hours of randomisation
- All-cause mortality within 30 days of randomisation
- Pre-hospital time and type and volume of fluid
- Vital signs (systolic blood pressure, heart rate, capillary oxygen saturation) at scene, on arrival at the Emergency Department (ED), then also at 2, 6, 12 and 24 hours after arrival at ED
- (Venous) lactate concentration on arrival at ED and at 2 hours after arrival at ED
- Trauma-induced coagulopathy (defined as International Normalised Ratio (INR) >1.5) to be measured on arrival at ED, and also at 2 and 6 hours after arrival at ED
- Coagulation measured viscoelastically by rotational thromboelastometry (ROTEM®)[VI]
- Platelet function using multiple electrode impedence aggregometery (MultiPlate)[VI]
- Total blood product receipt at 6, 12 and 24 hours after arrival at ED
- Acute respiratory distress syndrome (ARDS) within the first 7 days after injury
- Transfusion-related complications

[IV] Episode mortality refers to mortality between time of injury/ recruitment and discharge from the primary receiving facility to non-acute care, i.e. discharge home or to long-term care, to rehabilitation or repatriation to a hospital closer to their normal residence

[V] A patient is considered randomised and entered into the trial when the first intervention box has been opened.

[VI] Selected RHS only

- Organ failure-free days[30]. The presence of organ failure is defined as any Sequential Organ Failure Assessment (SOFA) component score[31] of ≥ 3. Organ failure will be assumed to be absent if the participant is discharged from hospital and will be assumed to be present if the participant has died

4. Eligibility

The Pre-Hospital Emergency Medical (PHEM) doctor will assess the potential participant's vital signs on scene and confirm if eligible for entry into the **RePHILL** trial.

4.1 Inclusion Criteria

- Traumatic injury
- Pre-Hospital Emergency Medical team attend
- Hypotension (Systolic Blood Pressure <90mmHg or absence of palpable radial pulse) believed to be due to traumatic haemorrhage

4.2 Exclusion Criteria

- Children (known or apparently aged <16 years)
- Blood administered on-scene, prior to arrival of the RePHILL PHEM team
- Refusal of blood product administration; known Jehovah's Witness
- Pregnancy (known or apparent)
- Isolated head injury without evidence of external haemorrhage
- Known prisoners in the custody of HM Prison or Probation services

5. Informed Consent Procedure

Major traumatic haemorrhage is a life-threatening condition that requires urgent treatment. **RePHILL** is a trial of a potentially life-saving intervention. The vast majority of eligible participants will lack capacity throughout the recruitment and intervention periods of the trial. An occasional participant may retain capacity; however their clinical condition will require immediate resuscitation. It would therefore be inappropriate to attempt to gain informed consent at this time as it would delay life-saving resuscitation. It is therefore impossible to obtain prospective informed consent. It would also be clinically unjustifiable to delay treatment until full informed consent can be obtained from a personal legal representative. Even if such a representative 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. Consequently **RePHILL** **cannot be conducted on the basis of prospective informed 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 clearly acknowledged in the Declaration of Helsinki 2008). Under UK law, emergency care is permitted under the terms of The Medicines for Human Use (Clinical Trials; Amendment No.2) Regulations 2006. Specifically:

- *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 Pre-Hospital Emergency Medical (PHEM) team will search the participant on scene for evidence that they would refuse participation, such as an Advance Directive, as carried by members of the Jehovah's Witness faith.

Contact with trial participants and/or their relatives/friends 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, the earliest practicable time to make contact is once the participant is no longer critically ill.

This trial will include consent to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink; CPRD, The Health Improvement Network; THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre (HSCIC) and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that may appear in the future. This will allow us to double check the main outcomes against routine data sources, and extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the trial participants. This is important as it will link a trial of treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which may not be collected during the period of the trial.

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 and version number of the informed consent form (ICF) signed and date consent received.

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 as appropriate) and documented in the medical notes, and the participant or legal representative 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 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.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be presented on the headed paper of the local institution. With the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

5.1 Participant Consent (*after* trial intervention)

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 all of 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.

5.2 Participants Who Lack Capacity to Consent for Themselves

Consent from a legal representative will be sought as soon as practically possible following the patient's admission to hospital. In the first instance, the local research team will work to identify a **personal legal representative** as defined below:

A personal legal representative is a person independent of the trial, who by virtue of their relationship with the trial participant is suitable to act as their legal representative for the purposes of the trial and who is available and willing to so act for those purposes.

The personal legal representative will be approached and will be provided with the REC approved personal legal representative information sheet explaining the trial and the options for the participant's continuing involvement, including the need for them to give consent on behalf of the participant. The personal legal representative will then have time to consider the information provided, after which, a member of the local research team will ask when the personal legal representative would like them to come back and discuss participation further and potentially receive consent.

The personal legal representative may decide that it is not an appropriate time to discuss the trial or they may decide that the participant would not want to take part, in which case their feelings will be respected and their decision about the participant continuing in the trial will be recorded.

In the event that a personal legal representative cannot be identified, the local research team will work to identify a **professional legal representative** as defined below:

A person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult. Or a person nominated by the relevant healthcare provider.

Informed consent given by a professional representative shall represent the participant's presumed will.

If the participant does regain capacity during the follow-up period, they will be asked to give consent for themselves using the process outlined in **Section 5.1**. The participant's wishes (consent or refusal) will supersede the personal or professional legal representative consent.

5.3 Consent Arrangements for Patients under the Age of 16

Children who are known or apparently aged <16 years are excluded from participating in the **RePHILL** Trial. However it is recognised that there may be scenarios where participants under the age of 16 are inadvertently randomised e.g., where they appear older than 16 years and do not have identification with them that confirms their actual age. In this scenario, consent will be sought, after the trial intervention, from a parent or guardian. If the participant has capacity, they

will also be asked to provide assent for their continued participation in the trial. A Parent/ Guardian Consent Form and an Assent Form (for participants <16 years) will be provided for this purpose.

5.4 Participants Who Do Not Survive

The most challenging ethical consideration in 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 publically 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 **RePHILL** trial and a REC approved poster will be placed in appropriate locations of the receiving hospitals.

For those participants that have been randomised, but subsequently die at scene, it will be impossible to obtain any form of consent. The data transferred to the BCTU for these participants will be pseudoanonymised with the trial number (this will be obtained when the **RePHILL** PHEM Case Report Form (CRF) has been completed) and if available, a partial date of birth. An Exit Form will also be completed for these patients, documenting partial date of death.

Should a participant die *en route* to hospital,, the participant will be transferred to the receiving hospital as per the standard process. During this time, a handover in the ED will take place and the **RePHILL** PHEM CRF and Exit Form will be completed. The data that are transferred to BCTU for these participants will also be pseudoanonymised with the trial number and if available, a partial date of birth.

6. Randomisation and Enrolment Process

6.1 Randomisation Process

Randomisation will be provided by a computer generated programme at the Birmingham Clinical Trials Unit (BCTU). Participants will be randomised at the level of the individual in a 1:1 ratio to either PHBP resuscitation or crystalloid resuscitation.. The randomisation procedure will be stratified by Intervention Delivery Site (IDS) to account for variation in trauma care and type of trauma between delivery sites.

6.1.1 Role of Blood Banks

The role of the blood bank in the **RePHILL** trial will be to maintain a constant supply of randomised trial interventions to the PHEM team. The blood bank will obtain the randomised allocations via a secure online system (available at: https://www.trials.bham.ac.uk/RePHILL) at the BCTU. Unique log-in usernames and passwords will be provided to the blood bank staff supporting the trial. The online system will be available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance. Alternatively, a back-up telephone toll-free allocation service on 0800 953 0274 is available Monday - Friday, 09:00-17:00. This excludes bank holidays and University of Birmingham closed days. If an online connection is not available, telephone allocation and a back-up paper allocation using a simple randomisation list will be used.

Blood banks will be supplied with pre-printed 'treatment box number' labels. A registered user at the blood bank will request a treatment allocation from the BCTU and will receive a treatment box number and treatment arm allocation. The allocated trial intervention will be packed into transport boxes affixing the correct labels. Transport boxes will be issued as a pair, one marked red and one marked yellow per single randomised allocation. The treatment box number should be identical on each coloured box pair carried. The date and time of expiry will also be written on each transport box.

The packed, sealed transport boxes will be dispatched to the PHEM base using an established courier service as required.

6.1.2 Role of PHEM

Upon receiving the box pairs from the blood bank, the PHEM team will need to access the RePHILL online system (https://www.trials.bham.ac.uk/RePHILL) and acknowledge receipt. As part of this process, the PHEM team will need to confirm that the boxes are matched, i.e. that they have the same number on both of them, that they are sealed and the time they were received.

During their shift, the PHEM team should ensure that they are carrying a pair of sealed, red and yellow transport boxes with matched box numbers.

Where possible, unopened transport boxes (with the seal still intact) should be returned to the blood banks prior to expiry, to minimise wastage. PRBC may be returned to stock and re-issued if there have been no temperature excursions.

6.2 Randomisation

The PHEM doctor will assess the potential participant's vital signs on scene and confirm if eligible for entry into the **RePHILL** trial. If they fulfil the eligibility criteria (as defined in Section 4 of the protocol) then the randomised treatment will be given. **Participants are considered randomised into the trial when the PHEM team open the first transport box containing the allocated trial intervention**. Eligibility will be documented at the Receiving Hospital Site (RHS) and the RePHILL PHEM Case Report Form (CRF) completed at handover in the ED. To receive a Trial Number, a member of the research team will access the online system at the BCTU and enter the information recorded on the PHEM CRF (Section 6.3).

6.3 Enrolment

Delegated site staff can enrol a participant (and obtain a trial number) by accessing the secure online system: https://www.trials.bham.ac.uk/RePHILL. In order to enrol a participant, site staff must have access to the completed 'Eligibility Checklist' and the 'Pre-Hospital Details' sections in the PHEM CRF. All fields must have been completed in order for the participant to be enrolled and a trial number issued.

6.4 Co-enrolment

Due to the emergency nature of this trial, it is highly unlikely that those randomising and enrolling patients to RePHILL will be aware if a patient is already participating in a clinical trial. Where a patient enrolled in RePHILL is subsequently found to have been participating in a concurrent trial, BCTU will inform the RePHILL CI, who will in turn liaise with the CI for the other trial.

When it is possible to plan in advance, the Trial Management Group (TMG) will consider requests for co-enrolment into other trials in accordance with best practice recommendations [32]. This will ensure careful consideration of patient burden, compatibility of interventions, organisational issues and follow-up. A log of co-enrolled patients will be maintained by BCTU.

6.5 Post Randomisation Exclusions and Withdrawals

Participants who are later found to be ineligible, but who have received the trial intervention will remain in the trial as per protocol and be included in the analysis.

For participants who have withdrawn consent for continuing in the trial, data already collected up until the point of withdrawal will be retained and included in the analysis.

7. Trial Procedures and Assessments

7.1 On-scene

The attending PHEM doctor will assess eligibility on-scene. Prior to delivery of the intervention eligible participants will have a capillary blood test taken to measure lactate concentration using a point-of-care lactate device. The capillary blood will be obtained by a finger prick on a test strip, no sample can be retained from this, and therefore no tissue will be stored as a result of this test.

The allocated intervention will then be administered as either:

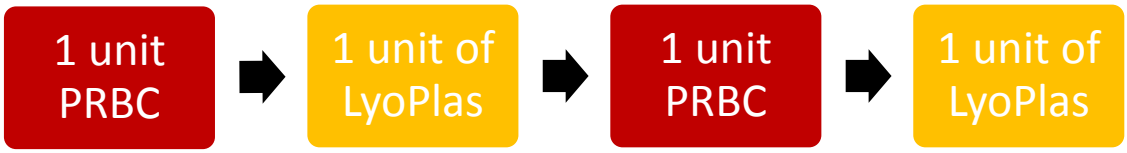
Crystalloid resuscitation:

- Consisting of up to 4 x 250 mL bags of 0.9% sodium chloride (normal saline). These will be administered as boluses of 250 mL to restore and maintain a systolic blood pressure (SBP) of ≥ 90 mmHg or a palpable radial pulse

OR

PHBP resuscitation:

- Consisting of up to 2 units of PRBC and 2 units of LyoPlas. These will be administered as boluses consisting of a single unit of blood product, given in the sequence:



(*The volume of 1 unit PRBC is 270 mL (range: 220 – 340). The volume of reconstituted LyoPlas is 213 mL. Consequently, over the 4 boluses, similar volumes of fluid are administered in each trial arm)*

In both arms, when possible, all interventions administered (normal saline, PRBC and LyoPlas) should be given through fluid warmers.

7.1.1 Subsequent Boluses

In both arms of the trial: if a SBP of ≥90 mmHg or a radial pulse returns after the administration of a bolus and remains present, no further fluid will be administered. If a SBP of ≥90 mmHg or the radial pulse does not return or if it is subsequently lost, further boluses will be administered until it is restored. In each case a maximum of 4 boluses can be administered as part of the trial interventions.

Any additional fluid boluses required to maintain blood pressure after administration of the 4 trial boluses should be given according to standard local practice.

7.1.2 Lactate Concentration

In cases where the participant is still on scene 2 hours after randomisation, a second capillary blood test should be taken to measure lactate concentration using a point-of-care lactate device at 2 hours after randomisation.

7.2 On Arrival at the Receiving Hospital ED

Trial data collected by the PHEM team will be shared with the RHS, in accordance with local policy and recorded on the RePHILL PHEM CRF.

7.2.1 Vital Signs

The following will be measured:

- Heart rate measured in beats per minute (bpm)
- Blood pressure measured in mmHg
- Respiratory rate is the number of breaths (inhalation – exhalation cycles) counted in one minute
- Capillary oxygen saturation (SpO_2) measured by application of a probe to a finger, toe or ear. SpO_2 is the percentage of haemoglobin that is oxygenated

7.2.2 Tissue Oxygenation and Perfusion

Selected sites only

When possible, Near-infra-red spectroscopy (NIRS) will be used to monitor tissue oxygenation and perfusion via a non-invasive adhesive pad attached to the participant's skin.

7.2.3 (Venous) Lactate Concentration

Lactate concentration will be measured on arrival at ED and 2 hours after arrival as part of standard care. **It will also be measured 2 hours after randomisation (if not previously done on scene), for trial purposes**. Where possible, a venous sample should be taken, however if this is not possible then an arterial sample is permitted. Lactate concentration will be measured on a near-patient blood gas analyser. There is no processing required before analysis. This is drawn as a normal part of trauma care (i.e. is no extra burden for the participant). The blood volume drawn

varies between syringes but is typically between 1 mL and 3 mL, to be drawn into a pre-heparinised syringe.

7.2.4 Calculating Lactate Clearance

Lactate clearance[33] is expressed as a percentage per hour (%/h) and is calculated from the measurement of (venous) lactate concentration (with automated analysers that are near-patient) by the PHEM team immediately prior to randomisation (Lac_0) and at 2 hours after randomisation (Lac_h) as:

$$\text{Lactate Clearance} = \frac{100 \times (Lac_0 - Lac_h)}{Lac_0 \times \text{Interval}}$$

7.2.5 Blood Samples on Admission

- Routine laboratory testing to include Full Blood Count (FBC), urea and electrolytes (U&Es) and bilirubin, coagulation and transfusion. Other tests to be included as clinically indicated
- The standard laboratory tests of coagulation are Clauss fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), International Normalised Ratio (INR). INR is a ratio of PT to normal, corrected for local processes and reagents, allowing valid comparison between different laboratories
- Transfusion testing to include ABO and RhD group with assessment for mixed field group, antibody screen and Direct Antiglobulin Test (DAT)

7.2.6 Blood Sampling for ROTEM®

Selected sites only

Coagulation will be measured viscoelastically by rotational thromboelastometery (ROTEM®):

- For sites using the ROTEM® machine, 4.5 mL of venous blood is to be drawn into a citrated container (BD Vacutainer 367691 or equivalent). The citrated container contains the additive sodium citrate which inhibits blood clotting. This is a standard tube for blood clotting tests. No pre-processing is required.
- EXTEM and FIBTEM tests will be performed.

7.2.7 Blood Sampling for Platelet Function

Selected sites only

Selected sites will have a platelet function analyser (MultiPlate)[34]. Three MultiPlate tests (using ADP, ASPI and TRAP agonists) will be carried out from a venous blood sample drawn into a 3 evacuated hirudin-coated blood tube (Sarstedt AG & Co. S-Monovette® 04.1944.001 or equivalent).

7.2.8 Blood Sampling for Future Research

Queen Elizabeth Hospital, Birmingham only

In anticipation of future studies, blood will be drawn for serum preparation and storage. A blood sample (1 x 5 mL) will be drawn into a pre-evacuated tube containing clot activator (BD Vacutainer 367986 or equivalent).

7.3 During Hospital Admission

The following assessments are to be made during the hospital admission as indicated by the participant's clinical condition, up to withdrawal, acute care discharge, death or day 30, whichever is earlier.

7.3.1 Acute Respiratory Distress Syndrome (ARDS)

This will be assessed at day 7. The Berlin definition of ARDS will be used for assessing participants[34]. Criteria for the diagnosis are shown in Table 1.

Table 1: Criteria for diagnosis of ARDS

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules
Origin	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation	PaO_2/FiO_2 ≤40 kPa with either PEEP or CPAP ≥5 cm H_2O (invasive or non-invasive)

7.3.2 Sequential Organ Failure Assessment score (SOFA) score

The extent of a participant's organ dysfunction will be recorded using the SOFA score[31]. The score is based on six components, one each for the following systems:

- Respiratory
- Neurological

- Cardiovascular
- Liver
- Coagulation
- Renal

The scores are assigned as shown in Tables 2 a-f.

The SOFA score will be determined daily for the duration of intensive care stay up to day 30. Scores will be derived from routine clinical and laboratory records.

Tables 2a-f: SOFA Score

Respiratory (a)

PaO_2/FiO_2 (kPa)	Score
≥53.3	0
<53.3	1
<40.0	2
<26.7 and mechanically ventilated	3
<13.3 and mechanically ventilated	4

Neurological (b)

Glasgow Coma Scale (GCS)	Score
15	0
13-14	1
10-12	2
6-9	3
<6	4

Cardiovascular (c)

Mean Arterial Pressure or inotrope requirement	Score
MAP ≥70 mmHg	0
MAP <70 mmHg	1
dop ≤5 or dob (any dose)	2
dop >5 OR epi ≤0.1 OR nor ≤0.1	3
dop >15 OR epi>0.1 OR nor >0.1	4

Key: dop: Dopamine, dob: dobutamine, epi: adrenaline, nor: noradrenaline
Doses in μg/kg/min

Liver (d)

Bilirubin (μmol/L)	Score
<20	0
20-32	1
33-101	2
102-204	3
>204	4

Coagulation (e)

Platelets×10^3/μl	Score
≥150	0
<150	1
<100	2
<50	3
<20	4

Renal (f)

Creatinine (μmol/L) or urine o/p	Score
≤109	0
110-170	1
171-299	2
300-440 (or <500 mL/day)	3
> 440 (or <200 mL/day)	4

7.4 Schedule of Assessments

Refer to Table 3 below:

Table 3: Table of Assessments

	On-scene	ED arrival	2 hours post-randomisation	2 hours post-ED arrival	6 hours post-ED arrival	12 hours post-ED arrival	24 hours post-ED arrival	During hospital stay (up to day 30)
Vital signs	✓	✓		✓	✓	✓	✓	
Confirm eligibility	✓							
[1]Lactate concentration	✓	✓	✓	✓				
Administer allocated treatment	✓							
Legal Representative Consent		✓						
Participant Consent								✓
[2]Blood sampling		✓		✓	✓			✓
ROTEM® (participating sites only)		✓						
Blood sampling (platelet function)		✓						
Record fluids administered	✓	✓		✓	✓	✓	✓	
Record surgical procedures				✓	✓	✓	✓	
SOFA and ARDS								✓
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓
[3]Date and time of death of non-survivors	✓	✓	✓	✓	✓	✓	✓	✓
[4]Acute care discharge date								✓

1 Capillary lactate concentrations taken on-scene will be measured using a simple point-of-care tester.

2 Standard laboratory tests should include a full blood count and coagulation tests. The normal sampling and laboratory practices of the site should be followed.

3 Mortality may extend beyond 30 days as it includes episode mortality

4 Acute care discharge date should be recorded following discharge from acute care. This may extend beyond 30 days.

8. Trial Intervention/Investigational Medicinal Products

8.1 Trial Treatments

8.1.1 PHBP Arm (Lyophilised Plasma LyoPlas N-w (LyoPlas) and PRBC)

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 the Marketing Authorisation Number PEI.H.03075.01.1, and therefore is being classified as an Investigational Medicinal Product (IMP) in the **RePHILL** trial.

PRBC are a concentrated preparation of red blood cells that is obtained from whole blood by removing the plasma (as by centrifugation).

The PRBC used in **RePHILL** will be blood group O, RhD negative, Kell negative from NHS Blood and Transplant national stocks supplied by the blood banks that are supporting this trial.

8.1.2 Crystalloid Arm

The crystalloid resuscitation comparator arm will consist of 0.9% sodium chloride (normal saline; a solution of sodium chloride in water). This is classified as the comparator IMP in the **RePHILL** trial.

8.2 Supply of Trial Stocks and Storage Conditions

8.2.1 Trial Supplies

LyoPlas

The trial stock of LyoPlas will be shipped from the central IMP distribution centre to local receiving site pharmacies. One packaged unit of LyoPlas will comprise:

- 1 glass bottle of 200 mL freeze dried human plasma
- 1 plastic bag containing 200 mL water for injection
- 1 transfer set

PRBC

The PRBC will be from national stocks supplied by the blood banks that are supporting the **RePHILL** trial.

Normal saline

Normal saline will be from routine NHS stock and does not require any special storage conditions.

8.2.2 Packaging and Labelling of the IMPs

LyoPlas: The central IMP distribution centre will package and label the LyoPlas prior to sending out to local site pharmacies.

Normal saline: Will be provided from local site pharmacies as standard NHS stock and will be labelled by site pharmacies prior to transfer to blood banks.

Both IMPs will be labelled in compliance with the applicable regulatory requirements.

8.2.3 Storage

LyoPlas is stable between 2°C – 25°C and should be maintained within these limits whilst stored in local pharmacies and blood banks..

For the **RePHILL** trial, once packaged into the trial intervention transport boxes, the LyoPlas should be maintained between 15°C and 25°C to permit ease of preparation and administration.

PRBC is to be maintained at 4°C (± 2°C) in accordance with blood bank standard procedures.
Normal saline should be stored in accordance with the Summary of Product Characteristics (SmPC).

8.3 Administration of Treatment

With respect to the interventions:

- LyoPlas may be administered via either an intravenous (IV) or intraosseous (IO) route after reconstitution in water, in accordance with the manufacturer's instructions.
- PRBC may be administered via either an intravenous (IV) or intraosseous (IO) route, according to standard clinical practice
- Normal saline may be administered via either an intravenous (IV) or intraosseous (IO) route, according to standard clinical practice

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

8.4 Interactions or Contraindications

LyoPlas and PRBC have been prepared with citrate, therefore solutions containing calcium must not be administered concurrently through the same line. Medicinal products should not be added to LyoPlas or PRBC. If an acute transfusion reaction (ATR), including allergic reactions, is suspected

following IV/IO infusion of either PRBC 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.

9. Pharmacovigilance

9.1 Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The Investigator will assess the seriousness and causality (relatedness) of all applicable AEs experienced by the participant with reference to the reference safety information. This should be documented in the source data.

Standard definitions of different types of AEs are listed in **Table 4a** and categorisation of causality shown in **Table 4b**.

Table 4a: Definition of standard terms

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which is related (or for which a causal relationship cannot be ruled out) to any dose administered to that subject
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product; (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
Serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR)	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death; • is life-threatening; • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; or consists of a congenital anomaly or birth defect
SUSAR	Suspected Unexpected Serious Adverse Reaction (as defined above)

Table 4b: Categorisation of causality

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events)
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 medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments)
Not related	There is no evidence of any causal relationship

In the **RePHILL** trial, the LyoPlas and normal saline are categorised as the IMPs and the pharmacovigilance reporting requirements that will be followed are described in this section of the protocol.

As this is a trial using an intervention that also includes a blood component (PRBC), the statutory arrangements for haemovigilance should also be followed (refer to **Section 9.7**).

AEs will be recorded in the medical records as per standard clinical practice. Most (S)AE/ARs that occur in this trial, whether they are serious or not, will be 'expected' treatment-related consequences of the trial intervention or trauma related.

9.2 (Serious) Adverse Events

RePHILL trial participants are likely to have significant co-morbidities and therefore the frequency of AEs is likely to be high. Most of the AEs occurring in **RePHILL**, 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 AEs that meet the definition of an SAE, other than the SAEs listed in **Section 9.2.1**

9.2.1 Events that do not Require Reporting on a SAE Form

The following are regarded as expected SAEs (i.e. are recognised complications/consequences of major trauma) for the purpose of this trial and should not be reported on an SAE Form. These events should be reported on the appropriate trial CRF(s) instead and will not be subject to expedited reporting.

Event	CRF
Death (from trauma)	Exit Form
Organ failure (single organ)	Daily Assessments
Multi organ dysfunction syndrome	Daily Assessments
Systemic inflammatory response syndrome	Daily Assessments
Acute respiratory distress syndrome	Daily Assessments – Day 7
Infection (any anatomical site)	Daily Assessments
Venous thromboembolism (deep venous thrombosis or pulmonary embolism)	Daily Assessments – Day 7
Transfusion reactions occurring after ED arrival	24 Hour FU and Daily Assessments

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

9.2.2 Monitoring Participants Pregnancies for Potential SAEs

Known pregnancy at the time of enrolment is an exclusion criterion for the **RePHILL** trial, however, should a participant later be found to have been pregnant at the time of trauma and received the trial intervention, the outcome of the pregnancy (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed-up and documented, even if the participant withdrew consent from follow-up within the trial. Initial notification of pregnancy will be done via a SAE form and the outcome of the pregnancy will be recorded on the Pregnancy Notification Form. These will be reported to the **RePHILL** Trial Office.

9.2.3 Reporting Period

Details of all SAEs (except those listed as excluded) will be documented and reported from the date of commencement of protocol defined treatment.

9.3 Reporting Procedure – Site

9.3.1 Serious Adverse Events

Receiving hospitals should report SAE's which are NOT listed as recognised complications of major trauma (as defined in section 9.2.1), to the **RePHILL** Trial Office on a SAE Form as soon as possible and no later than 24 hours after becoming aware of the event.

Complete SAE Forms should be faxed to the **RePHILL** Trial Office on:

0121 415 9135 or 0121 415 9136

The research team at site will be required to respond to any related queries raised by the **RePHILL** Trial Office as soon as possible.

Site Investigators should also notify their own institutions of any SAEs in accordance with their institutional policies.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the categorisation of seriousness and causality assessments. The SAE Form should then be returned to the **RePHILL** Trial Office and a copy retained at site.

9.3.2 Provision of Follow-up Information

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

9.4 Reporting Procedure – Trial Office

On receipt of the SAE form, the **RePHILL** Trial Office will allocate each SAE a unique reference number which will be forwarded to the receiving hospital as proof of receipt. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE.

On receipt of an SAE Form, seriousness and causality will be reviewed independently by the Chief Investigator (CI; or nominated delegate). A 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. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the approved version of the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.5 Reporting to the Competent Authority and Research Ethics Committee

9.5.1 Suspected Unexpected Serious Adverse Reactions

The **RePHILL** Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and REC within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

A copy will be sent to the Trial Sponsor at the time of sending the SUSAR report.

9.5.2 Serious Adverse Reactions

The **RePHILL** Trial Office will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).
A copy will also be sent to the Sponsor at the time of sending out the DSUR.

9.5.3 Other Safety Issues Identified during the Course of the Trial

The MHRA, REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

9.6 Investigators

Details of all SUSARs and any other safety issue(s) which arise during the course of the trial will be reported to Principal Investigators (PI). A copy of any such correspondence should be filed in the Investigator Site File (ISF).

9.7 Haemovigilance

Staff at IDS will be responsible for reporting all transfusion-related adverse events 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 EU Blood Safety Directive[35, 36]. Similarly, the receiving hospital staff are also responsible for reporting all transfusion-related adverse events, including acute transfusion reactions (<24 hr) and delayed transfusion reactions (>24 hr), to SHOT/SABRE according to standard procedures.

Each individual blood bank issuing blood will have 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 blood bank is different from the issuing hospital blood bank, then both parties should co-ordinate to ensure traceability and reporting.

The hospital blood transfusion laboratory that provided the PRBC (coordinating blood bank) 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 blood bank.

9.8 Developmental Safety Update Reports

The **RePHILL** Trial Office will provide the MHRA with DSURs. The reports will be submitted within 60 days of the Development International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9.9 Annual Progress Reports

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 is declared ended. A copy will also be sent to the Sponsor at the time of sending out the DSUR.

9.10 Reporting Urgent Safety Measures

If any urgent safety measures are taken, the CI/BCTU shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the circumstances giving rise to those measures.

9.11 Notification of Serious Breaches of Good Clinical Practice and/or the Protocol

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of Good Clinical Practice (GCP) in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify the **RePHILL** Trial office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the **RePHILL** Trial office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

The BCTU on behalf of the Sponsor shall notify the MHRA and REC in writing of serious breaches.

10. Data Management and Quality Assurance

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

10.2 Data Collection

During the hospital admission, up to withdrawal, discharge from acute care, death or day 30 (whichever is earlier), where possible, outcome data will be extracted from participant's clinical notes and laboratory reports, to complete the **RePHILL** trial CRFs (**Table 5**).

Table 5: RePHILL Trial CRFs

Form Name	Schedule for Submission
PHEM CRF	As soon as possible following admission
ED Admission CRF	As soon as possible following admission
Confirmation of Consent Form	As soon as possible following admission
2, 6, 12 and 24 hour Follow-Up CRFs	As soon as possible after each time point
ROTEM CRF	As soon as possible after each time point
Impedance Aggregometry and NIRS CRF	As soon as possible after each time point
Daily Assessments	As soon as possible
Medical History CRF	When a full medical history for the participant is available
Exit Form	Where applicable, as soon as possible after exit event
Serious Adverse Event Form	Faxed within 24 hours of research site becoming aware of event
Pregnancy Notification Form	When outcome information on the pregnancy is available

It is the responsibility of the Investigator to ensure the accuracy of all data entered in the CRFs. The **RePHILL** Trial Signature and Delegation Log will identify all those personnel with responsibilities for data collection. The Trial Office must be informed immediately of any change in the site research team.

Prior to commencing recruitment all sites will undergo a process of initiation and will have completed GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

The CRFs will comprise, but will not necessarily be limited to those listed in Table 5.

If paper CRFs are being completed, they must be signed and dated and returned to the **RePHILL** Trial Office by the PI or an authorised member of the site research team (as delegated on the **RePHILL** Trial Signature & Delegation Log) within the timeframe listed in the table above. Entries on paper CRFs should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change. Data reported on each CRF should be consistent with the related source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All sections should be completed; all missing and ambiguous data will be queried. In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. Paper CRFs received will be entered onto the trial database by a trained member of the BCTU trial team.

If remote electronic data entry is being undertaken then CRFs should be entered online at: https://www.trials.bham.ac.uk/RePHILL. Authorised staff at IDS and RHS will require an individual secure login username and password to access this online data entry system. As above, data reported should be consistent with the related source data and all missing and erroneous data will be queried.

CRF version numbers may be updated by the **RePHILL** Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

It will be the responsibility of the PI to ensure the accuracy of all data entered in the CRFs. The RePHILL Trial Signature and Delegation Log will identify all those personnel with responsibilities for data collection.

Access to data, including the final trial dataset will be limited to the Research Team.

The investigator(s)/ institution(s) will permit trial-related monitoring, audits REC review and regulatory inspection(s), providing direct access to source data/ documents. Trial participants are informed of this during the informed consent discussion and will consent to provide access their medical notes.

11. Statistical Considerations

11.1 Sample Size

Although no definitive data exists on this composite outcome, the observational studies suggest potentially dramatic reductions in mortality from civilian pre-hospital PRBC[21] and military pre-hospital PRBC with thawed plasma[17]. Following extensive consultation with experts in pre-hospital trauma resuscitation, it is considered that an absolute reduction of 10% in the proportion of patients experiencing one of the component primary outcomes is clinically meaningful for the patients and is an appropriate effect size upon which to base the power calculation.

To detect an absolute difference of 10% between groups in the proportion of patients experiencing either episode mortality or lactate clearance <20%/h in the two hours post-randomisation (i.e. from 20% in the standard care group to 10% in the group receiving PHBP) using the method of difference between proportions (2-sided Fisher's Exact Test) with 80% power, and a type 1 error rate of 5% (i.e. α=0.05), requires 219 participants per group to be randomised, 438 participants in total. Assuming and adjusting for a 10% loss to follow-up rate, 490 participants will need to be recruited.

11.2 Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those resuscitated with PHBP versus those resuscitated with normal saline. All analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the groups to which they were allocated irrespective of compliance with the randomised treatment allocation or other protocol violation. For all major outcome measures, summary statistics and differences between groups (e.g. mean differences, relative risks, hazard ratios) will be presented, with 95% confidence intervals and p-values from two-sided tests also given. The data will be assessed for normality and appropriate data transformations or non-parametric tests will be used if necessary. Outcomes will be adjusted for the minimisation variable, IDS, where possible. A p-value of <0.05 will be considered statistically significant, and no adjustment for multiple comparisons will be made.

11.2.1 Primary Outcome Analysis

The primary outcome is a composite measure of episode mortality[VII] and early lactate clearance (see section 7.2.4 for formula for calculating lactate clearance) and is measured as a binary outcome. Participants clearing less than 20% per hour of their lactate between randomisation and 2 hours after randomisation or dying will be defined as experiencing the primary outcome. A log-binomial regression model, adjusting for IDS, will be used to calculate the relative risk and 95% confidence interval. As this is a composite endpoint, it will also be reported in accordance with the recommendations of Ferreira-González et al[37].

11.2.2 Secondary Outcome Analysis

Dichotomous data (e.g. development of ARDS, mortality at specified time-points) will be analysed in the same way as the primary outcome. Survival data (e.g. mortality) will be analysed using the log-rank test with a Cox Proportional Hazard model used to calculate hazard ratios, if the assumptions of proportionality are met. Continuous outcomes (e.g. pre-hospital fluid volume, vital signs) will be analysed at specified time-points using linear regression models, with mean differences and 95% confidence intervals reported.

[VII] Episode mortality refers to mortality between time of injury/ recruitment and discharge from the primary receiving facility to non-acute care, i.e. discharge home or to long-term care, to rehabilitation or repatriation to a hospital closer to their normal residence.

11.2.3 Subgroup Analyses

Eleven a priori subgroup analyses are planned with respect to both the primary and secondary outcome measures. The subgroups will be IDS, mode of transport (air .vs. ground), initial lactate concentration (≤ 2.2 mmol/L .vs. >2.2 mmol/L), time to ED from injury (≤ 1 hour .vs. >1 hour), mode of injury (blunt, penetrating, crush), volume of pre-hospital fluid given (total intervention 4 units) vs. those not receiving the total intervention), age (<50 years, 50-70 years, >70 years), head injury (positive vs. negative), compressible haemorrhage (compressible haemorrhage vs. non-compressible haemorrhage), pre-morbid drug history (anticoagulant or antiplatelet medication vs. no anticoagulant or antiplatelet medication) and age of blood products (<8 days vs. ≥ 8 days). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimates within subgroups. The results of subgroups will be treated with caution and will be used for the purposes of hypothesis generation only.

11.2.4 Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants, it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, missing responses will be simulated using a Markov chain Monte Carlo method (MCMC) to generate multiple datasets. Analysis will be then be performed on each set with the results combined using Rubin's rule to obtain a single set of results (treatment effect estimate and confidence intervals). Any sensitivity analyses will not, irrespective of their differences, supplant the planned primary analyses. Full details will be included in the SAP.

11.3 Planned Interim Analyses

Interim analyses of major outcome measures and safety data will be conducted and provided in strict confidence to the independent DMC (see section 17.3). Details of the agreed plan will be written in the SAP.

11.4 Planned Final Analyses

The final analysis for the study will occur once all participants have completed the trial as per the end of trial definition and corresponding outcome data has been entered onto the study database and validated as being ready for analysis.

12. End of Trial

For participants, the main trial data collection ends at withdrawal, acute care discharge, death, or at 30 days follow-up, whichever occurs first. Apart from episode mortality data which will be collected up to discharge from an acute care setting, which may be >30 days.

The end of trial will be 30 days after the date of last data capture (to include resolution of missing data and data queries). The **RePHILL** Trial Office will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the **RePHILL** Trial Office will inform the MHRA and REC within 15 days of the end of trial. The **RePHILL** Trial Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report will also be sent to the Sponsor at the time of sending these to the MHRA and REC.

13. Archiving

All essential documents within the Trial Master File will be archived for up to 25 years after completion of the trial. Electronic data sets will be stored indefinitely.

It is the responsibility of the Principal Investigators at sites to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

14. Direct Access to Source Data

The investigator(s)/institution(s) will permit trial-related monitoring, quality checks, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify the **RePHILL** Trial Office of any MHRA inspections.

Trial participants who regain capacity will be informed of this during the informed consent discussion and will consent to provide access to their clinical notes. Personal or legal representatives will be informed of this during the informed consent discussion where consent is

being sought due to lack of participant capacity and will also consent to provide access to the participant's clinical notes for these purposes.

15. Ethics and Regulatory Requirements

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998.

This trial will be carried out under a Clinical Trial Authorisation (CTA) in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. Monitoring Requirement

Monitoring of **RePHILL** will ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of **RePHILL** will be adopted and outlined in the trial-specific risk assessment.

The **RePHILL** Trial Office will be in regular contact with the site research team to check on progress and address any queries that they may have. The Trial Office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants giving explicit consent.

Additional on-site monitoring visits may be triggered, for example poor CRF return, poor data quality, excessive number of deviations. This will be detailed in the monitoring plan. If a monitoring

visit is required, the **RePHILL** Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the RePHILL trial staff access to source documents as requested.

17. Oversight Committees

17.1 Trial Management Group

The TMG will comprise the CI, other lead investigators (clinical and non-clinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of **RePHILL**. It will convene at regular intervals.

17.2 Trial Steering Committee (TSC)

The role of the TSC is to provide the overall supervision of the trial. The TSC will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMEC. Further details of the remit and role of the TSC are available in the TSC Charter.

17.3 DMEC

An independent DMEC will be established to oversee the safety of participants in the trial. The DMEC will meet prior to the trial opening to enrolment and again once the first 25 patients have been entered into the study or at the end of the 6 month internal pilot trial part, whichever occurs first, to assess the safety data, and advise on continuation to the main phase III trial (see Section 3.2 for the Internal Pilot Stopping Rules). Since this is an internal pilot trial, and this safety data will be included in the main analysis of the **RePHILL** trial, this data will remain confidential, except to members of the DMEC and the trial statistician(s) performing the analysis.

During the main phase III trial, the DMEC will meet at least annually, or as per a timetable agreed by the DMEC prior to trial commencement. Data analyses will be supplied in confidence to the DMEC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMEC will operate in accordance with the trial specific charter.

If one treatment really is substantially better or worse than the other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than the other. To protect against this, during the main period of recruitment

to the trial, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMEC, along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) "proof beyond reasonable doubt"[VIII] that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

18. Finance

The National Institute for Health Research (NIHR) Efficacy & Mechanism Evaluation Programme is funding this trial (project number 14/152/14).

19. Indemnity

This is a clinician-initiated study. There are no special arrangements to provide compensation for non-negligent harm to participants. The "Clinical Trial Compensation Guidelines" published by the ABPI will not apply.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the organisation where they were treated.

Non-NHS organisations taking part in the study and NHS organisations who are not members of their appropriate national clinical negligence scheme (for example CNST in England, CNORIS in Scotland) must take out adequate insurance, or provide other indemnity satisfactory to the sponsor, to cover their potential liabilities against claims for negligence, and must be able to provide evidence of the cover if requested by the sponsor. The University of Birmingham has in force, a public liability policy and/ or clinical trials policy which provides cover for claims of 'negligent harm' and the activities here are included in that coverage.

[VIII] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least p<0.001 (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

20. Dissemination and publication

Regular newsletters will keep collaborators informed of trial progress, and regular meetings will be held to report progress of the trial and to address any problems encountered in the conduct of the trial.

The CI will coordinate dissemination of data from **RePHILL.** All publications and presentations, including abstracts, relating to the main trial will be authorised by the **RePHILL** TMG. The results of the analysis will be published in the name of the **RePHILL** Trial Investigators in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified. Trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper. All applications from groups wanting to use **RePHILL** data to undertake original analyses will be submitted to the TMG for consideration before release. To safeguard the scientific integrity of **RePHILL**, trial data will not be presented in public before the main results are published without the prior consent of the TMG.

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