Surgical Reconstruction and Microbiology Research Centre

NHS National Institute for Health Research

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

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

Trial Registration: ISRCTN 62326938

Statistical Analysis Plan

SAP Version Number	Protocol Version Number
1 0	3 0

Name of Author:	Jon Bishop	Role:	Trial Statistician	Affiliation:	BCTU University of Birmingham
Signature of Author:		Date:			
Name of Chief Investigator:	Prof Gavin Perkins	Role:	Chief Investigator	Affiliation:	Warwick Medical School and University Hospitals Birmingham NHS Foundation Trust
Signature of Chief Investigator:		Date:	28 Jun 2021		
This Statistical Analysis Plan has been approved by:					
Name of Approver:	Natalie Rowland	Role:	Senior Statistician	Affiliation:	BCTU University of Birmingham
Signature of Approver:		Date:			

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim/final analysis/database lock	Blind Reviewer	
				Name:	
				Signature:	
				Date:	
				Name:	
				Signature:	
				Date:	
				Name:	
				Signature:	
				Date:	

Statistical Analysis Plan (SAP) Amendments

Abbreviations & Definitions	
Abbreviation / Acronym	**Meaning**
ARDS	Acute respiratory distress syndrome
BCTU	Birmingham Clinical Trials Unit
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
ED	Emergency Department
GCS	Glasgow Comma Score
HDI	Highest Density Interval
IDS	Intervention Delivery Site
INR	International Normalised Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
MCMC	Markov Chain Monte Carlo
OOR	Out of Range
PHBP	Pre-Hospital Blood Products
PHEM Team	Pre-Hospital Emergency Medical Team
PRBC	Packed Red Blood Cells
PT	Prothrombin Time
RHS	Receiving Hospital Site
ROTEM®	Rotational Thromboelastometry
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
Term	**Definition**
International Standard Randomised Controlled Trial Number	A clinical trial registry
Protocol	Document that details the rationale, objectives, design, methodology and statistical considerations of the study
Randomisation	The process of assigning trial subjects to intervention or control groups using an element of chance to determine the assignments in order to reduce bias
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either in the protocol or in a separate document

TABLE OF CONTENTS

1. Introduction 7
2. Background and rationale 7
3. Trial objectives 7
4. Trial methods 8
4.1. Trial design 8
4.2. Trial interventions 8
4.3. Primary outcome measure 8
4.4. Secondary outcome measures 8
4.5. Timing of outcome assessments 9
4.6. Randomisation 9
4.7. Sample size 10
4.8. Framework 11
4.9. Interim analyses and stopping guidance 11
4.10. Internal Pilot Progression Rules 12
4.11. Timing of final analysis 12
4.12. Timing of other analyses 12
4.13. Trial comparisons 12
5. Statistical Principles 12
5.1. Confidence intervals and p-values 12
5.2. Adjustments for multiplicity 13
5.3. Analysis populations 13
5.4. Definition of adherence 13
5.5. Handling protocol deviations 13
5.6. Unblinding 14
6. Trial population 14
6.1. Recruitment 14
6.2. Baseline characteristics 14
7. Interventions 14
7.1. Description of the interventions 14
7.2. Adherence to allocated intervention 14
8. Protocol deviations 14
9. Analysis methods 15
9.1. Covariate adjustment 15
9.2. Distributional assumptions and outlying responses 15
9.3. Handling missing data 15
9.4. Data manipulations 16
9.5. Analysis methods - primary outcome(s) 20
9.6. Analysis methods - secondary outcomes 21
9.7. Analysis methods - exploratory outcomes and analyses 21
9.8. Safety data 22
9.9. Planned subgroup analyses 23
9.10. Sensitivity analyses 24
10. Analysis of sub-randomisations 25
11. Health economic analysis 25
12. Statistical software 25
13. References 25
Appendix A: Deviations from SAP 27
Appendix B: Trial schema 28
Appendix C: Schedule of assessments 29
Appendix D1: CONSORT flow diagram 30
Appendix D2: Baseline characteristics 31

Appendix D2a: Prehospital timeline by group 33
Appendix D2b: Mode of transport by IDS 34
Appendix D3: Description of the interventions 34
Appendix D4: Adherence to allocated intervention 34
Appendix D5: Protocol deviations 35
Appendix D6: Primary outcome results 35
Appendix D6a: Qualifying event for primary outcome 36
Appendix D7: Secondary outcomes results 37
Appendix D8: Safety 40
Appendix D9: Subgroup analysis for primary outcome 41
Appendix D10: Exploratory Bayesian analysis for primary outcome 42
Appendix D10a: Exploratory Bayesian analysis for episode mortality 43
Appendix D10b: Exploratory Bayesian analysis for lactate clearance 43

1. Introduction

This document is the Statistical Analysis Plan (SAP) for the RePHILL trial, and should be read in conjunction with the current trial protocol This SAP details the proposed analyses and presentation of the data for the main paper(s) reporting the results for the RePHILL trial

The results reported in these papers will follow the strategy set out here Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here The principles are not intended to curtail exploratory analysis (e g to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (e g transformation of data prior to analysis), but they are intended to establish rules that will be followed, as closely as possible, when analysing and reporting data

Any deviations from this SAP will be described and justified in the final report or publication of the trial (using a table as shown in Appendix A) The analysis will be carried out by an appropriately qualified statistician, who should ensure integrity of the data during their data cleaning processes

2. Background and rationale

The background and rationale for the trial are outlined in detail in the protocol In brief, 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 Acceptance of in-hospital haemostatic resuscitation saw the British military implement it for battlefield casualty retrieval With the increasing adoption of giving Pre-Hospital Blood Products (PHBP) for trauma in both the UK and abroad, in both military and civilian settings, it is important to determine whether this intervention is effective The provision of PHBP requires considerable logistical and financial resources and RePHILL will establish a high quality evidence base for PHBP resuscitation

3. Trial objectives

The primary objective 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

Secondary objectives are to test the hypotheses that, when compared to standard care, does PHBP resuscitation:

I. Improve blood pressure, heart rate and capillary oxygenation on Emergency Department (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 (ARDS)?
VIII. Lead to blood product wastage?
IX. Affect haemoglobin concentration levels on ED arrival?

4. Trial methods

4.1. Trial design

RePHILL is a multi-centre, prospective, open-label, superiority, parallel group, phase III randomised controlled trial with an internal pilot phase See Appendix B for trial schema The progression rules for the internal pilot are described in section 4 10

Participants will be recruited at the scene of their traumatic injury

4.2. Trial interventions

PHBP (Lyophilised Plasma LyoPlas N-w (LyoPlas) and PRBC) resuscitation vs crystalloid (0 9% sodium chloride [normal saline]) resuscitation (standard care)

4.3. Primary outcome measure

The primary outcome is a composite measure consisting of episode mortality (mortality between time of injury/recruitment and discharge from the primary receiving facility to non-acute care) and lactate clearance An event is defined as either episode mortality or a failure to achieve lactate clearance of ≥20% per hour in the first 2 hours after randomisation where a participant is considered randomised and entered into the trial when the first intervention box has been opened

4.4. Secondary outcome measures

Secondary outcomes are as follows:

- 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 ED, then also at 2, 6, 12 and 24 hours after arrival at ED
- Haemoglobin concentration on ED arrival

- (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
- Total blood product receipt at 6, 12 and 24 hours after arrival at ED
- ARDS within the first 7 days after injury
- Transfusion-related complications
- Organ failure-free days The presence of organ failure is defined as any Sequential Organ Failure Assessment (SOFA) component score of ?3 Organ failure will be assumed to be absent if the participant is discharged from acute care and will be assumed to be present if the participant has died

At selected receiving hospital sites (RHS) the following secondary outcomes will also be recorded:

- Coagulation measured viscoelastically by rotational thromboelastometry (ROTEM®)
- Platelet function using multiple electrode impedence aggregometery (MultiPlate)

4.5. Timing of outcome assessments

The schedule of trial procedures and outcome assessments are given in the protocol Secondary outcome measures will be assessed on at least one of the following time points: on-scene; 3 hours post randomisation; arrival at ED; 2, 6, 12, and 24 hours after arrival at ED; and daily assessments up to day 30

4.6. Randomisation

Participants will be randomised at the level of the individual in a 1:1 ratio to either PHBP (Lyophilised Plasma LyoPlas N-w (LyoPlas) and PRBC) resuscitation or crystalloid (0 9% sodium chloride [normal saline]) resuscitation

Randomisation will be performed centrally at the Birmingham Clinical Trials Unit (BCTU) using stratification by intervention delivery site (IDS) to account for variation in trauma care and type of trauma between delivery sites

In the RePHILL trial, the blood banks will maintain a constant supply of randomised trial interventions to the Pre-Hospital Emergency Medical (PHEM) team The blood bank will obtain the randomised allocations via a secure online system at the BCTU

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 packed, sealed transport

boxes will be dispatched to the PHEM base using an established courier service as required

On-scene, 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 for the trial, 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

4.7. Sample size

Although no definitive data exists on the composite primary outcome measure, observational studies suggest potentially dramatic reductions in mortality from civilian pre-hospital PRBC[1] and military pre-hospital PRBC with thawed plasma[2] Following extensive consultation with experts in pre-hospital trauma resuscitation, it is considered that an absolute reduction of 10% in the proportion of participants experiencing one of the component primary outcomes is clinically meaningful for the participants 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 participants 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 a=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

The interim analysis for the Data Monitoring Committee (DMC) meeting in May 2018 reported the results on the 192 participants recruited by 20th April 2018 A pooled event rate of 65% experiencing either episode mortality or lactate clearance <20%/h in the two hours post-randomisation was observed in these participants This observed rate does not correspond with the pooled event rate of 15% assumed in the original sample size calculations On the DMCs recommendations, this issue was discussed with the TSC in October 2018 The TSC recommended that the power calculations were framed in terms of a relative risk rather than an absolute risk, with the original target sample size of 490 unchanged

Assuming the pooled event rate remains at 65% and allowing for a 10% loss to follow-up rate, 490 participants will provide 80% power to detect a relative risk ratio of 0 82 (i e from 71 7% in the standard care group to 58 3% in the group receiving PHBP) using the method of difference between proportions (2-sided Fisher's Exact Test), and a type 1 error rate of 5% (i e a=0 05) This estimated relative risk ratio is consistent with the relative risk ratios of 1 54[3] and 0 70[4] reported in two recent pre-hospital randomised controlled trials using plasma in one of the treatment arms

4.8. Framework

The objective of the trial is to test the superiority of one intervention to another

The null hypothesis is that there is no difference in the composite outcome of either episode mortality or a failure to achieve lactate clearance ≥20% per hour in the first 2 hours after randomisation between the intervention groups The alternative hypothesis is that there is a difference between the groups

4.9. Interim analyses and stopping guidance

A separate DMC reporting template will be drafted and agreed by the DMC including an agreement on which outcomes will be reported at interim analyses The statistical methods stated in this SAP will be followed for the outcomes included in the DMC report, where possible

If PHBP resuscitation is substantially better or worse than crystalloid resuscitation with respect to the composite outcome of episode mortality or lactate clearance, then this may become apparent before the target recruitment has been reached Alternatively, new evidence might emerge from other sources to suggest that PHBP resuscitation is definitely more, or less, effective than crystalloid resuscitation To protect against any unnecessary continuation of the trial, interim analyses of major endpoints and safety data will be supplied, in strict confidence, to the independent DMC, along with updates on results of other related studies, and any other analyses that the DMC may request

The DMC will advise the chair of the Trial Steering Committee (TSC) if, in their view, any of the randomised comparisons in the trial have provided both: a) "proof beyond reasonable doubt"t that for all, or for some, types of participant one particular intervention is definitely indicated or definitely contra-indicated in terms of a net difference of a major endpoint; 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 Unless this happens, however, the TSC, the collaborators and all of the central trial staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results

t 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[5] stopping boundary) in an interim analysis of a major endpoint may be required 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 Given the proposed use of the Haybittle-Peto boundary, no adjustment for multiple testing (to control the overall type I error rate) is proposed, i e the threshold for statistical significance at the final analysis will still be p=0 05

4.10. Internal Pilot Progression Rules

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;
- DMC reports no safety concerns, which would prohibit continuation to main trial

The pilot data was reviewed by the DMC and TSC on 26/APR/2017 and the trial was allowed to continue

4.11. Timing of final analysis

The final analysis for the trial will occur once all the participants have completed the trial The main trial data collection for participants ends at withdrawal, discharge to non-acute care, death or at 30 days follow-up, whichever occurs first Apart from episode mortality data which is collected up to discharge from acute care which may be >30 days Final analysis will then occur only after the corresponding outcome data has been entered onto the trial database and validated as being ready for analysis This is provided that the trial has not been stopped early for any reason (e g DMC advice or funding body request)

4.12. Timing of other analyses

Not applicable

4.13. Trial comparisons

All references in this document to 'group' refer to PHBP (Lyophilised Plasma LyoPlas N-w (LyoPlas) and PRBC) or crystalloid (0 9% sodium chloride [normal saline]) resuscitation

5. Statistical Principles

5.1. Confidence intervals and p-values

All estimates of differences between groups will be presented with two-sided 95% confidence intervals, unless otherwise stated P-values will be reported from two-sided tests at the 5% significance level

5.2. Adjustments for multiplicity

No correction for multiple testing will be made

5.3. Analysis populations

All primary analyses (primary and secondary outcomes including safety outcomes) will be based on the intention-to-treat (ITT) principle Participants will be analysed in the intervention group to which they were randomised, and all participants shall be included whether or not they received the allocated intervention This is to avoid any potential bias in the analysis

A per protocol analysis will be carried out as a sensitivity analysis and will only be performed for the primary outcome Adherence and the per protocol group are defined in section 5 4

Further details on the sensitivity analyses are given in section 9 10

5.4. Definition of adherence

Adherence to allocated intervention will be monitored by recording the administration of each of the four trial interventions and reasons why any of the trial interventions were not given Blood banks will also monitor receipt of unused trial interventions upon return of the transport boxes

We will define adherence, in the crystalloid arm of the trial, as the administration of at least one bolus of fluid In the PHBP arm, adherence is defined as the administration of at least one unit of PRBC and one unit of LyoPlas Non-adherence will be defined as the failure to administer at least one bolus of fluid in the crystalloid arm or the failure to administer at least one unit of PRBC and one unit of LyoPlas in the PHBP arm without clinical justification (e g deemed not to be needed clinically, or, patient arrives at ED before the second bolus can be administered, etc)

The 'per protocol' population will include only those participants considered adherent to allocated intervention as described above

5.5. Handling protocol deviations

A protocol deviation is defined as a failure to adhere to the protocol such as errors in applying the inclusion/exclusion criteria, the incorrect intervention being given, incorrect data being collected or measured, follow-up visits outside the visit window or missed follow-up visits We will apply a strict definition of the ITT principle and will include all participants as per the ITT population described in section 5 3 in the analysis in some form, regardless of deviation from the protocol [6] This does not include those participants who have specifically withdrawn consent for the use of their data in the first instance; however these outcomes will be explored as per other missing responses

5.6. Unblinding

Not applicable, RePHILL is an open-label study

6. Trial population

6.1. Recruitment

A flow diagram (as recommended by CONSORT[7]) will be produced to describe the participant flow through each stage of the trial This will include information on the number (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial A template for reporting this is given in Appendix D1

6.2. Baseline characteristics

The trial population will be tabulated as per Appendices D2, D2a and D2b Categorical data will be summarised by number of participants, counts and percentages Continuous data will be summarised by the number of participants, mean and standard deviation if deemed to be normally distributed or number of participants, median and interquartile range if data appear skewed, and ranges if appropriate Tests of statistical significance will not be undertaken, nor confidence intervals presented [8]

7. Interventions

7.1. Description of the interventions

Not applicable

7.2. Adherence to allocated intervention

A cross-tabulation of allocated intervention by the adherence categories stated in section 5 4 will be produced (proportions and percentages) A template for reporting adherence is given in Appendix D4

8. Protocol deviations

Frequencies and percentages by group will be tabulated for the protocol deviations as per Appendix D5

9. Analysis methods

9.1. Covariate adjustment

In the first instance, intervention effects between groups for all outcomes will be adjusted for IDS (stratification variable; see section 4 6) as a fixed effect (this will be the primary analysis) A secondary analysis adjusting for IDS and the following prognostic variables (age, lactate, cardiac arrest and Glasgow Comma Score (GCS) at randomisation) as fixed effects will also be undertaken for the primary outcome measure (and the individual components)

For binary outcomes, if the log-binomial model fails to converge, a Poisson regression model with robust standard errors will be used to estimate the same parameters [9] If this also fails to converge, unadjusted estimates will be produced from the log-binomial model It will be made clear in the final report why this occurred (e g not possible due to low event rate/lack of model convergence)

Longitudinal secondary outcomes (e g vital signs, venous lactate concentration, etc) will also be adjusted for their baseline values

9.2. Distributional assumptions and outlying responses

Distributional assumptions (e g normality of regression residuals for continuous outcomes) will be assessed visually prior to analysis; although in the first instance the proposed primary method of estimation in this analysis plan will be followed If responses are considered to be particularly skewed and/or distributional assumptions violated, the impact of this will be examined through sensitivity analysis; this will consist of transformation of responses prior to analysis (e g log transformation) in the first instance If extreme values are apparent and considered to be affecting the integrity of the analysis, a sensitivity analysis consisting of removing the outlying response(s) and repeating the analysis will be performed Output from these analyses, if performed, will be described and presented alongside the original analysis (or included, e g in appendices) with the excluded values clearly labelled

9.3. Handling missing data

In the first instance, analysis will be completed on received data only with every effort made to follow-up participants to minimise any potential for bias To examine the possible impact of missing data on the results, and to make sure we are complying with the intention-to-treat principle, sensitivity analysis will be performed on the primary outcome measure [10] See section 9 10 for further details regarding planned sensitivity analyses

9.4. Data manipulations

The Trial Statistician will derive all responses from the raw data recorded in the database

Age

This is the number of years that occur between the date of randomisation and the date of birth and is obtained using the INTCK function in SAS v9 4 The trial only collects partial date of birth (i e only month and year) so it will be assumed that the participant was born on the 15th day of the month

Date and time of randomisation

This is defined as the date and time at which the first treatment box was opened

Time on scene

This is the number of minutes that occur between the date and time of on-scene attendance and the date and time of ED arrival, and is obtained using the INTCK function in SASv9 4 Values are reported in minutes

Lactate clearance

The value, date, and time of the 2 hour post-randomisation lactate concentration are the value, date, and time of either the:

a) Capillary lactate concentration taken if the participant has not reached hospital within 2 hours of randomisation, or the
b) Venous lactate concentration taken in ED if the participant has reached hospital within 2 hours of randomisation, or the
c) Arterial lactate concentration taken in ED if the participant has reached hospital within 2 hours of randomisation and venous access is not available

The lactate concentration value available from a) to c) above which is closest to the 2 hours from randomisation time point will be used as the 2 hour lactate concentration value regardless of method of collection

Using the following notation:

	=	Randomisation capillary lactate concentration
	=	2 hour post-randomisation lactate concentration
	=	Date and time of
	=	Date and time of
Interval	=	- (in minutes)

The interval time is given by:

Time between 2 hour post -randomisation lactate concentration and randomisation lactate (minutes)	=	Date and Time of the 2 hour post-randomisation lactate concentration ()	-	Date and Time of the randomisation capillary lactate concentration ()

Lactate clearance, expressed as a percentage per hour (%/h), is calculated using the formula:

A normal lactate is taken to be s2 2 mmol/L Achieving ?20% per hour lactate clearance is defined as follows in participants whose:

a) is >2 2 mmol/L and whose demonstrates lactate clearance of ?20% per hour; or
b) is >2 2 mmol/L, but whose is s2 2 mmol/L, regardless of the magnitude of the change; or
c) and are both s2 2 mmol/L, regardless of the magnitude and direction of any difference

All the above will be counted as participants achieving ?20% per hour lactate clearance

The above can be summarised in the following table:

(mmol/L)	(mmol/L)	Required lactate clearance
>2 2	>2 2	?20% per hour
>2 2	s2 2	Not applicable
s2 2	s2 2	Not applicable

Achieving <20% per hour lactate clearance is defined as follows in participants:

a) Whose is >2 2 mmol/L and whose demonstrates lactate clearance of <20% per hour; or
b) Who die prior to interval sampling (e g before the measurement is taken at) For this we require the date and time of death from the exit form to determine if the participant died within two hours and 30 minutes of randomisation

The table below summarises what is considered an event (failure to achieve lactate clearance):

(mmol/L)	(mmol/L)	Lactate clearance <20% per hour	Lactate clearance 220% per hour
>2 2	>2 2	Failure to clear (event)	Achieves clearance
>2 2	s2 2	Achieves clearance	Achieves clearance
s2 2	s2 2	Achieves clearance	Achieves clearance
Dies prior to interval sampling and within 2 5 hours of randomisation		Failure to clear (event)	

There are instances where the lactate value is too high for a value to be reported, i e the value is out of range (OOR) of the detection level of the test In these cases, the lactate measurement is recorded on the database as "too high to be recorded" In these instances, at database lock prior to analysis, a review of these lactate values will undertaken independently by two statisticians blind to treatment allocation to assess whether the participant cleared their lactate or not For example, if randomisation lactate is OOR, but the 2 hour randomisation lactate is

s2 2, then as per the table above the participant would be considered to have achieved clearance; or if both the randomisation and 2 hour lactates are OOR, then the participant will be considered to have failed to clear If unable to determine, then the lactate component of the primary outcome will be considered missing

Episode Mortality

Episode mortality is defined as those participants who die during the study between time of injury/recruitment and discharge from the primary receiving facility to non-acute care (this includes participants who die on-scene) The date of discharge from acute care and date of death are recorded on the exit form Any deaths occurring after the date of discharge from acute care are not considered to be cases of episode mortality

Primary Outcome

The primary outcome is a composite measure consisting of episode mortality (mortality between time of injury/recruitment and discharge from the primary receiving facility to non-acute care) and lactate clearance (failure to achieve lactate clearance ?20% per hour in the first two hours from randomisation) Therefore, if the participant experiences either:

a) episode mortality or
b) a failure to achieve lactate clearance ?20% per hour in the first 2 hours after randomisation

they will be considered to have experienced the primary outcome If they have survived to the point of exiting the trial through discharge from acute care and have experienced lactate clearance ?20% per hour in the first 2 hours after randomisation they will be considered to not have experienced the primary outcome

All-cause mortality within 3 hours of randomisation

The time to death is calculated by (Date and Time of death - Date and Time of randomisation) If this is less than or equal to 3 hours then the participant will be coded as having experienced all-cause mortality within 3 hours of randomisation (i e s3 hours) If this is more than 3 hours (i e >3 hours), or if the participant has completed the exit form through discharge from acute care then the participant will be coded as not having experienced all-cause mortality within 3 hours of randomisation If the Date and Time of death is not recorded, but the participant is known to have died on-scene, then it will be assumed that the participant experienced all-cause mortality within 3 hours of randomisation

All-cause mortality within 30 days of randomisation

The time to death is calculated by (Date of death - Date of randomisation) If this is less than or equal to 30 days then the participant will be coded as having experienced all-cause mortality within 30 days of randomisation (i e s30 days) If this is more than 30 days (i e >30 days), or if the participant has completed the exit form through discharge from acute care (i e was alive at discharge from acute care) then the participant will be coded as not having experienced all-cause mortality within 30 days of randomisation If the Date and Time of death is not recorded,

but the participant is known to have died on-scene, then it will be assumed that the participant experienced all-cause mortality within 30 days of randomisation

Trauma-induced coagulopathy

A participant is considered to have experienced trauma-induced coagulopathy if the INR>1 5 If no INR value has been recorded, the value of prothrombin time (PT) will be converted to an INR value and used instead To convert PT to an INR, the ratio of the observed patient PT to a control PT (standardized for the potency of the thromboplastin reagent) will be calculated:

This calculation requires the control PT to be known

Organ failure-free days (OFFS)

The presence of organ failure is defined as any SOFA component score of 3 Organ failure will be assumed to be absent if the participant is discharged from acute care and will be assumed to be present if the participant has died

The SOFA component scores are determined from the raw values using the conversions in Tables (a)-(f) below For each daily assessment organ failure is present if:

ANY(Respiratory, Neurological, Cardiovascular, Liver, Coagulation, Renal) 3

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 s5 or dob (any dose)	2
dop >5 OR epi s0.1 OR nor s0.1	3
dop >15 OR epi>0.1 OR nor >0.1	4

Liver (d)

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

Key: dop: Dopamine, dob: dobutamine, epi: adrenaline, nor: noradrenaline
Doses in [l]g/kg/min

Coagulation (e)

Plateletsx10^3/µl	Score
≥150	0
<150	1
<100	2
<50	3
<20	4

Renal (f)

Creatinine (µmol/L) or urine o/p	Score
s109	0
110-170	1
171-299	2
300-440 (or <500 mL/day)	3
> 440 (or <200 mL/day)	4

Then OFFS is the number of days alive and free of organ failure in the first 30 days Days in which a participant is on a ward will be defined as being organ failure free For the respiratory component, days in which a participant is either on a ward or in level 2 critical care will be defined as being ventilator free

Age of Blood Products

For each participant allocated to the PHBP, the age of each unit of administered blood products is calculated by (Date bled – Date of randomisation) If any unit is 8 days or older, that participant will be classified as receiving blood products ≥8 days old for the purposes of the subgroup analysis (see Section 9 9)

Cardiac Arrest

Participants will be classified as experiencing cardiac arrest if they have a heart rate of 0 and a blood pressure reading (systolic or diastolic) of 0 when their vital signs are recorded on-scene

9.5. Analysis methods - primary outcome(s)

A template for reporting the primary outcome is given in Appendix D6

The primary outcome is a composite measure of episode mortality or failure to clear lactate 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 between time of injury/recruitment and discharge to non-acute care will be defined as experiencing the primary outcome The primary outcome measure will be summarised as the number of participants experiencing the primary outcome with percentages

Adjusted relative risks (adjusted for IDS) along with 95% confidence intervals will be estimated using a log-binomial regression model Statistical significance of the treatment group parameter

will be determined from the p-value generated by the model The absolute risk difference along with 95% confidence intervals will be estimated using a binomial regression model with identity link As this is a composite endpoint, the primary outcome will also be reported in accordance with the recommendations of Ferreira-Gonzalez et al [11], with the qualifying event for the primary outcome presented using the template in Appendix D6a

See section 9 1 for details on covariate adjustment and model convergence

9.6. Analysis methods - secondary outcomes

A template for reporting the secondary outcomes is given in Appendix D7

Binary outcomes (e g development of ARDS, mortality at pre-specified time-points) will be analysed in the same way as the primary outcome

Continuous outcomes (e g pre-hospital fluid volume, vital signs, OFFS) will be summarised using means and standard deviations, or medians and IQRs if appropriate Adjusted mean differences (adjusted for IDS and baseline values) along with 95% confidence intervals will be estimated using a linear regression model Statistical significance of the treatment group parameter will be determined from the p-value generated by the model

9.7. Analysis methods - exploratory outcomes and analyses

Bayesian analysis of the primary composite outcome measure, and each component separately, will be performed as exploratory analyses to quantify the probability of treatment effects of different sizes The PHBP and Crystalloid intervention arms will be modelled separately, with the outcome assumed to be a random deviate from a Bernoulli distribution Priors will take the form of independent beta(a,) distributions and are set to model the probability of a participant achieving the primary outcome in each arm Three sets of priors are specified: non-informative priors, skeptical priors such that the probability of observing a treatment effect at least as large as the specified relative risk ratio of 0 82 is less than 5%, and informative priors reflecting current knowledge For each set of the priors, the table below provides the values of the shape parameters used to specify the beta distributions, summary statistics (mean, variance, median, upper and lower 2 5% quantiles), and simulated probabilities of exceeding three different treatment effect sizes (expressed as relative risk ratios)

	Priors					
	Non-informative		Skeptical		Informative	
	Crystalloid	PHBP	Crystalloid	PHBP	Crystalloid	PHBP
a	1	1	50	50	7	3
f3	1	1	25	25	3	2
Mean	0 5	0 5	0 667	0 667	0 7	0 6

Variance	0 0833	0 0833	0 003	0 003	0 019	0 04
2.5%	0 025	0 025	0 557	0 557	0 400	0 194
Median	0 5	0 5	0 668	0 668	0 714	0 614
97.5%	0 975	0 975	0 768	0 768	0 925	0 932
Pr(RR$0.82)	0 410		0 0442		0 444	
Pr(RR$0.70)	0 350		0 0015		0 313	
Pr(RR21.54)	0 325		0 0002		0 054	

For example, the informative prior for the PHBP group is set as beta(3,2), reflecting the assumption that the primary outcome rate in the PHBP group is unlikely to be lower than 19% or greater than 93% For the Crystalloid group, the informative prior is set as beta(7,3), reflecting the assumption that the primary outcome rate in the Crystalloid group is unlikely to be lower than 40% or greater than 93% Relative risk ratios of 1 54[3] and 0 70[4] were reported in two recent pre-hospital RCTs using plasma in one of the treatment arms The informative priors are specified such that the probabilities of observing treatment effects less than or equal to 0 70 and greater than or equal to 1 54 are 31 3% and 5 4% respectively Under the sceptical priors these probabilities are 0 15% and 0 02% respectively

Adjusted relative risks (adjusted for IDS), along with 95% highest density intervals (HDIs) will be estimated using a Bayesian log-binomial regression model The posterior probabilities that the relative risk ratio was less than 1, 0 8, and 0 7 will be calculated Similarly, risk differences, adjusted for IDS, along with 95% HDIs will be estimated using a Bayesian binomial regression model with an identity link The posterior probabilities that the risk difference was less than 0%, 10%, and 20% will be calculated A template for reporting is given in Appendices D10 to D10b

9.8. Safety data

The number and percentage of participants experiencing any adverse events, serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be presented by intervention group Statistical significance will be determined by a chi-squared test The total number of SAEs in each group will also be given along with a descriptive table of the details of the events A template for reporting this data is given in Appendix D8

9.9. Planned subgroup analyses

Interpretation of subgroup analysis will be treated with caution (output will be treated as exploratory rather than definitive[12]) Analysis will be limited to the primary outcome of a composite measure consisting of episode mortality and lactate clearance only, and the following subgroups:

- IDS
- Mode of PHEM transport (air vs ground)
- Initial lactate concentration (s2 2 mmol/L vs >2 2 mmol/L)

- Time to ED from injury (≤1 hour vs >1 hour)
- Mode of injury (blunt vs penetrating vs crush)
- Volume of pre-hospital fluid given (total intervention (4 boluses) vs <4 boluses)
- 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)
- Age of blood products (<8 days vs ≥8 days)
- Cardiac arrest (arrested vs not arrested)

The effects of these subgroups will be examined by including a treatment group by subgroup interaction parameter in the regression model. A template for reporting the subgroups analyses for the primary outcome is given in Appendix D9

The anticipated magnitude and direction of differential treatment effects in each of the subgroup analyses are:

- IDS: regional differences in PHEM protocols and system characteristics may alter the effect of the intervention. However, the anticipated direction of effect is unclear in the subgroup analysis for IDS and this analysis will be regarded as purely exploratory
- Mode of PHEM transport (air vs ground): ground transport typically takes longer than air transport, thus a greater effect of intervention may be observed in those being transported by ground
- Initial lactate concentration (≤2 2 mmol/L vs >2 2 mmol/L): participants with an abnormal initial lactate concentration (>2 2 mmol/L) may have a higher incidence of the primary outcome event and may exhibit a greater benefit from PHBP
- Time to ED from injury (≤1 hour vs >1 hour): participants taking >1 hour to arrive in ED from injury take longer to receive definitive treatment. Thus, a greater effect of intervention may be observed in participants taking more than >1 hour to arrive and receive definitive treatment in ED
- Mode of injury (blunt vs penetrating vs crush): the anticipated direction of effect is unclear in the subgroup analyses for mode of injury and this analysis will be regarded as purely exploratory
- Volume of pre-hospital fluid given (total intervention (4 boluses) vs <4 boluses): the volume given is considered a surrogate for the volume of blood loss. Participants receiving <4 boluses of pre-hospital fluid may have experienced less blood loss and a lower incidence of the primary outcome event. Thus, they may exhibit a reduced effect from PHBP
- Age (<50 years, 50-70 years, >70 years): mortality is greater in the more elderly groups. Therefore, the intervention is anticipated to have a greater effect in the >70 years cohort

- Head injury (positive vs negative): Major haemorrhage increases the risk of secondary brain injury We anticipate that the intervention effect may be greater in those with head injury
- Compressible haemorrhage (compressible haemorrhage vs non-compressible haemorrhage): the anticipated direction of effect is unclear in the subgroup analyses for compressible haemorrhage and this analysis will be regarded as purely exploratory
- Pre-morbid drug history (anticoagulant or antiplatelet medication vs no anticoagulant or antiplatelet medication): the degree of haemorrhage will be greater in those with anticoagulation medication Therefore, we anticipate that the intervention may have a greater effect in those participants on anticoagulant medication
- Age of blood products (<8 days vs ?8 days): fresh blood has better oxygen carrying capacity than old blood, therefore we anticipate that the intervention may have a greater effect in those participants receiving fresher blood (<8 days old)
- Cardiac Arrest: participants experiencing a cardiac arrest may have a higher incidence of the primary outcome event, but may be less likely to demonstrate any differential treatment effect due to the severity of their condition

9.10. Sensitivity analyses

Sensitivity analyses will be limited to the primary outcome and will consist of:

- Analysis adjusting for IDS and age, lactate, cardiac arrest and GCS at randomisation;
- Per-protocol analysis (population described in sections 5 3 and 5 4);
- An analysis to assess the effect of lactate timings Lactate clearance is calculated on measurements made at randomisation and 2 hours post-randomisation For this sensitivity analysis, time windows will be applied to the lactate measurements The lactate concentration at randomisation will only contribute to this analysis if the measurement was taken no more than 15 minutes (i e s15 minutes) before the PHEM team open the first transport box containing the allocated trial intervention The lactate concentration at 2 hours post randomisation will only contribute to this analysis if the measurement was taken within 30 minutes of the 2 hour assessment (i e between 1 5 and 2 5 hours post-randomisation) Lactate concentrations recorded outside these times will not be included in this sensitivity analysis
- An analysis to assess the effect of missing responses; missing responses will be simulated using a Markov chain Monte Carlo method (MCMC) to generate multiple datasets The imputation model will include the following variables: IDS, age, randomisation lactate, cardiac arrest, GCS, haemorrhage type, category of injury (penetrating, blunt, crush), heart rate, systolic blood pressure, and injury severity score 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) Each component of the primary outcome will be imputed separately[13,14]
- An analysis to assess the generalisability of the results by comparing baseline characteristics of those who are lost to follow-up or withdrawn from the trial with the trial

population

- An analysis to assess the generalisability of the results by comparing baseline characteristics of those who provide primary outcome data to those who do not provide primary outcome data

10. Analysis of sub-randomisations

Not Applicable

11. Health economic analysis

No health economic analysis is planned for this trial

12. Statistical software

Statistical analysis will be undertaken in the following statistical software packages: SAS v9 4 and RStan v2 19

13. References

1 Brown, J B , Cohen, M J , Minei, J P , Maier, R V , West, M A , Billiar, T R , Peitzman, A B , Moore, E E , Cuschieri, J and Sperry, J L Pretrauma center red blood cell transfusion is associated with reduced mortality and coagulopathy in severely injured patients with blunt trauma Annals of Surgery 2015; 261(5): 997-1005

2 O'Reilly, D J , Morrison, J J , Jansen, J O , Apodaca, A N , Rasmussen, T E and Midwinter, M J Prehospital blood transfusion in the en route management of severe combat trauma: A matched cohort study Journal of Trauma and Acute Care Surgery 2014; 77(3 Suppl 2): S114-20

3 Moore HB, Moore EE, Chapman MP, et al Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial Lancet 2018;392:283-91

4 Sperry JL, Guyette FX, Brown JB, et al Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock N Engl J Med 2018;379:315-26

5 Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV et al Design and analysis of randomised clinical trials requiring prolonged observation of each patient I Introduction and design Br J Cancer 1976;34:585-612

6 Gupta SK Intention-to-treat concept: A review Perspect Clin Res 2011;2(3):109-112

7 Schulz KF, Altman DG, Moher D, for the CONSORT Group CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials BMJ 2010;340:c332

8 Altman DG, Dore CJ Randomisation and baseline comparisons in clinical trials Lancet 1990;335:149-53

9 Zou G A modified Poisson regression approach to prospective studies with binary data Am J Epidemiol 2004;159(7):702-6

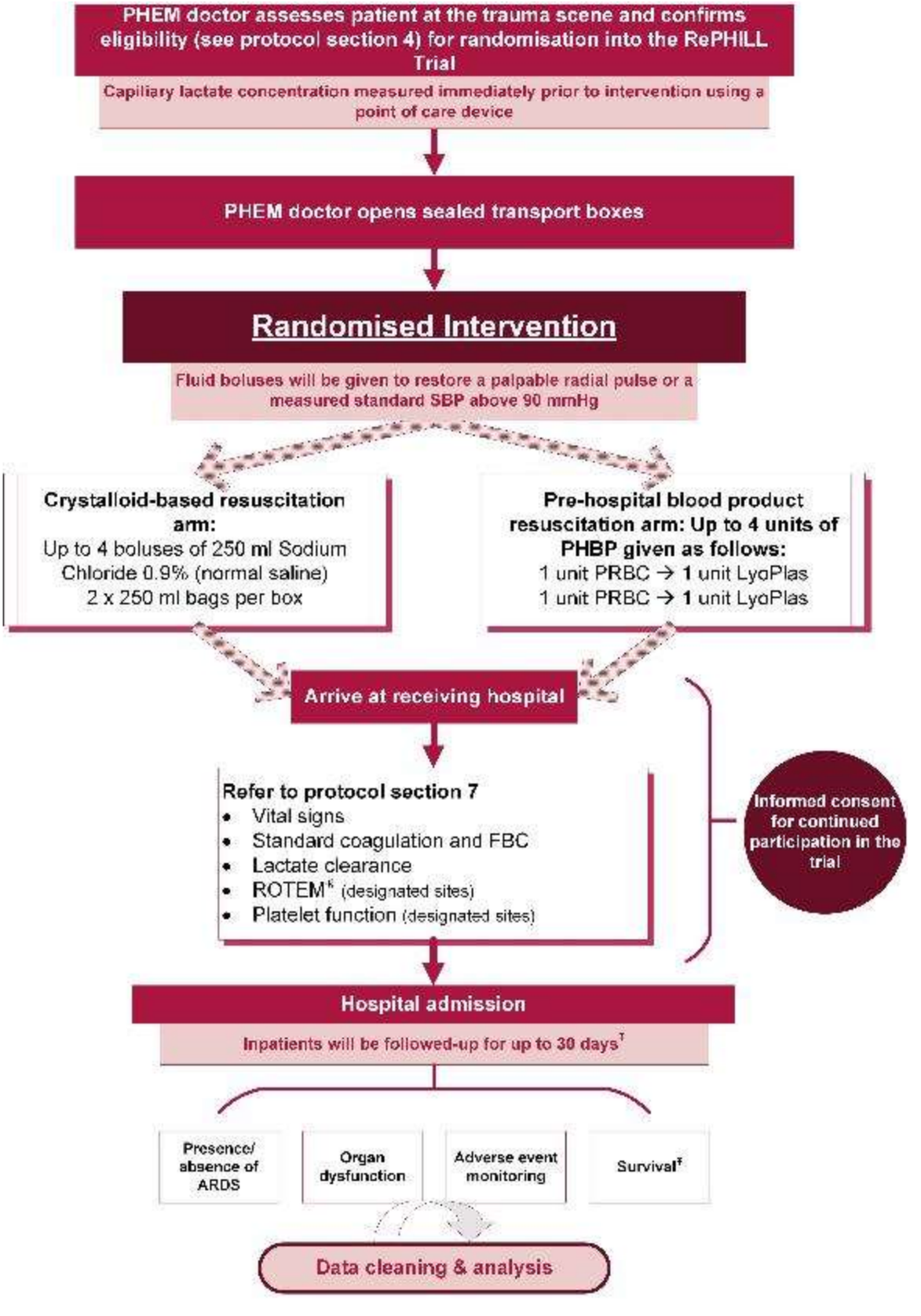
10 White IR, Horton NJ, Carpenter J, Pocock SJ Strategy for intention to treat analysis in randomised trials with missing outcome data BMJ 2011;342:d40
11 Ferreira-Gonzalez, I , Permanyer-Miralda, G , Busse, J W , Bryant, D M , Montori, V M , Alonso-Coello, P , Walter, S D and Guyatt, G H Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns Journal of Clinical Epidemiology 2007; 60(7): 651-7
12 Wand R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM Reporting of subgroups analyses in clinical trials NEJM 2007;357:2189-94
13 O'Keeffe AG, Farewell DM, Tom BD, Farewell VT Multiple imputation of missing composite outcomes in longitudinal data Statistics in biosciences 2016 Oct 1;8(2):310-32
14 Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ Should multiple imputation be the method of choice for handling missing data in randomized trials? Statistical methods in medical research 2018 Sep;27(9):2610-26

Appendix A: Deviations from SAP

This report below follows the statistical analysis plan dated <insert effective date of latest SAP> apart from following:

Section of report not following SAP	Reason
<insert section >	<insert, e.g. exploratory analyses request by TMG>

Appendix B: Trial schema

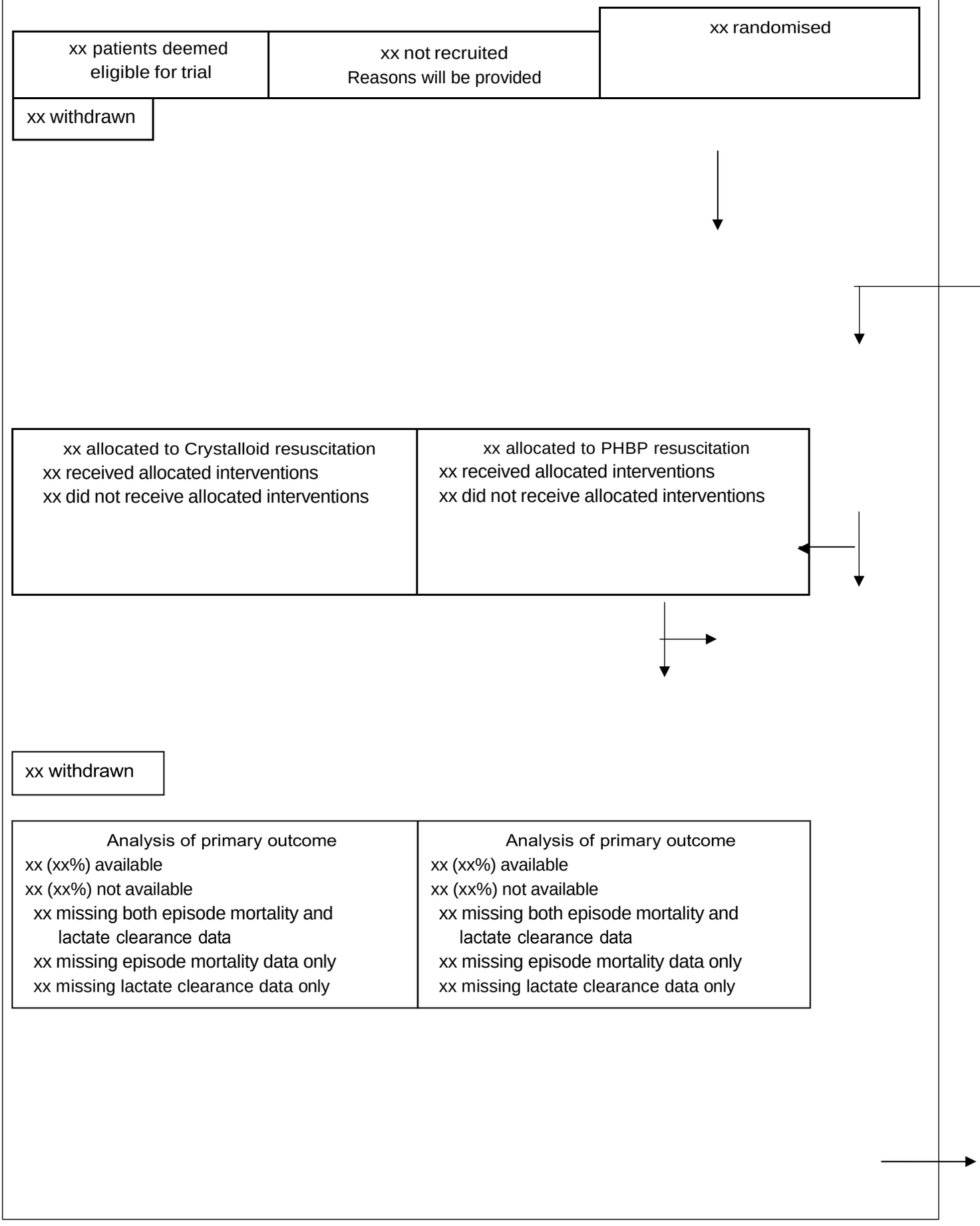


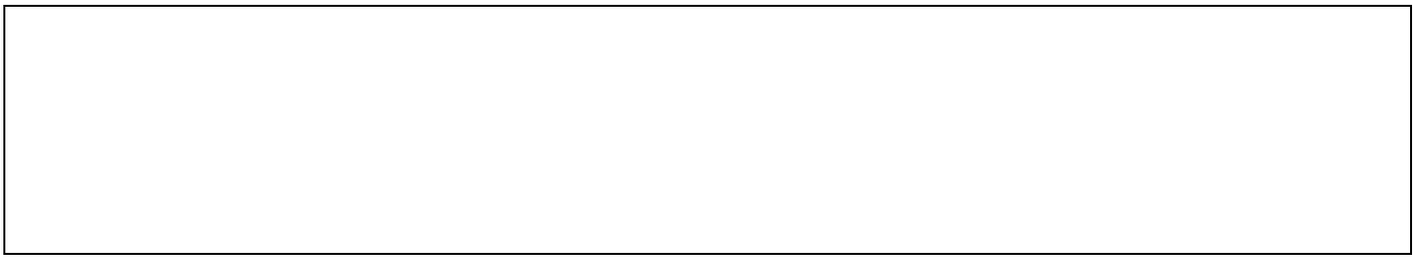
[†] Episode mortality data will be collected up to discharge from the acute care setting which may be >30 days

Appendix C: Schedule of assessments

See trial protocol

Appendix D1: CONSORT flow diagram





Appendix D2: Baseline characteristics

		PHBP (n=xxx)	Crystalloid (n=xxx)	Overall (n=xxx)
Stratification variable				
Intervention Delivery Site	Midlands Air Ambulance (MAA)	n (%)	n (%)	n (%)
	MAGPAS	n (%)	n (%)	n (%)
	The Air Ambulance Service (TAAS)	n (%)	n (%)	n (%)
	East Anglian Air Ambulance (EAAA)	n (%)	n (%)	n (%)
Demographic and other baseline variables				
Gender	Male	n (%)	n (%)	n (%)
	Female	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Age, years	Mean (SD)			
	Missing	n (%)	n (%)	n (%)
Ethnic Group, n (%)	White (British)	n (%)	n (%)	n (%)
	White (Irish)	n (%)	n (%)	n (%)
	White (Other)	n (%)	n (%)	n (%)
	Black (Caribbean)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Capillary lactate concentration (mmol/L)	Mean (SD)			
	Missing	n (%)	n (%)	n (%)
Mechanism of injury(ies) (More than one can apply)	Fall from <2m	n (%)	n (%)	n (%)
	Fall from ≥2m	n (%)	n (%)	n (%)
	Inhalation	n (%)	n (%)	n (%)
	Road traffic accident	n (%)	n (%)	n (%)
	Burn injury	n (%)	n (%)	n (%)
	Head Injury	n (%)	n (%)	n (%)
	Gunshot wound	n (%)	n (%)	n (%)
	Stabbing	n (%)	n (%)	n (%)
	Other	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Acute Brain Injury	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Mode of transport	Air	n (%)	n (%)	n (%)
	Ground	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Haemorrhage	Compressible	n (%)	n (%)	n (%)
	Non-compressible	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Category of injury	Blunt	n (%)	n (%)	n (%)
	Penetrating	n (%)	n (%)	n (%)
	Crush	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Tranexamic Acid				
Has the participant been given a tranexamic acid bolus?	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
On-scene Vital Signs				
Systolic Blood Pressure[1] (mmHg)	Zero	n (%)	n (%)	n (%)
	Non-zero	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)

	Mean (SD)			
Diastolic Blood Pressure[1] (mmHg)	Zero	n (%)	n (%)	n (%)
	Non-zero	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
	Mean (SD)			
Heart Rate[1] (bpm)	Zero	n (%)	n (%)	n (%)
	Non-zero	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
	Mean (SD)			
Respiratory Rate[1] (/min)	Zero	n (%)	n (%)	n (%)
	Non-zero	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
	Mean (SD)			
Cardiac Arrest[2]	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Capillary oxygen saturation (SpO_2) (%)	Mean (SD)			
	Missing	n (%)	n (%)	n (%)
GCS	Median (IQR)			
	Missing	n (%)	n (%)	n (%)
Suspected at time of injury	Alcohol	n (%)	n (%)	n (%)
	Other illicit substances	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Medical History				
ISS[3]	Median (IQR)			
	Missing	n (%)	n (%)	n (%)
NISS[3]	Median (IQR)			
	Missing	n (%)	n (%)	n (%)
Comorbidities	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Anticoagulant medication	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Unknown	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Antiplatelet medication	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Unknown	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)

[1] Systolic blood pressure, Heart rate and Respiratory rate are summarised as continuous variables only for participants with non-zero on scene measurements

[2] Defined at those with a heart rate of 0 and blood pressure of 0

[3] ISS and NISS will only be available for those participants who are TARN eligible, hence the number of missing participants refers to the number of TARN eligible participants missing their ISS or NISS.

Appendix D2a: Prehospital timeline by group

The duration in minutes between the time of the 999 call and prehospital events. Values above the diagonal correspond to the PHBP group and values below the diagonal correspond to the Crystalloid group.

Prehospital event	999 Call	On-scene attendance	Randomisation Capillary Lactate	Treatment box opening	Left Scene*	Arrival at ED**
999 call		Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR)	Median (IQR)

					(n N)	(n N)
On-scene attendance	Median (IQR) (n N)		Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)
Randomisation Capillary Lactate	Median (IQR) (n N)	Median (IQR) (n N)		Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)
Treatment box opening	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)		Median (IQR) (n N)	Median (IQR) (n N)
Left Scene*	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)		Median (IQR) (n N)
Arrival at ED**	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	Median (IQR) (n N)	

*Added in v4.0 of pre-hospital CRF (active in all sites from 29th August 2019)

**These numbers are lower than the totals of randomised participants due to deaths on-scene or during transit to hospital.

Appendix D2b: Mode of transport by IDS

Mode of transport	Midlands Air Ambulance (MAA) (N=)	MAGPAS (N=)	The Air Ambulance Service (TAAS) (N=)	East Anglian Air Ambulance (EAAA) (N=)	
Air	n (%)	n (%)	n (%)	n (%)	
Ground	n (%)	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	n (%)	

Appendix D3: Description of the interventions

Not applicable

Appendix D4: Adherence to allocated intervention

		PHBP	Crystalloid	Total
Number received intervention (n)[1]				
	Yes, n(%)	n (%)	n (%)	n (%)
	No, n(%)	n (%)	n (%)	n (%)
	Missing, n(%)	n (%)	n (%)	n (%)
No. units of PRBC given				
	0, n(%)	n (%)		n (%)
	1, n(%)	n (%)		n (%)
	2, n(%)	n (%)		n (%)
	Missing, n(%)	n (%)		n (%)

No. units of LyoPlas given				
	0, n(%)	n (%)		n (%)
	1, n(%)	n (%)		n (%)
	2, n(%)	n (%)		n (%)
	Missing, n(%)	n (%)		n (%)
No. units of saline given				
	0, n(%)		n (%)	n (%)
	1, n(%)		n (%)	n (%)
	2, n(%)		n (%)	n (%)
	Missing, n(%)		n (%)	n (%)
Total number of units given (n)				
	0, n(%)	n (%)	n (%)	n (%)
	1, n(%)	n (%)	n (%)	n (%)
	2, n(%)	n (%)	n (%)	n (%)
	3, n(%)	n (%)	n (%)	n (%)
	4, n(%)	n (%)	n (%)	n (%)
	Missing n(%)	n (%)	n (%)	n (%)
Total number of units given (n)				
	All 4 units, n(%)	n (%)	n (%)	n (%)
	1-3, n(%)	n (%)	n (%)	n (%)
	No units, n(%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
Per-protocol population (n)				
Received at least one unit of allocated intervention[2], n(%)	Yes, n(%)	n (%)	n (%)	n (%)
	No, n(%)	n (%)	n (%)	n (%)

[1] This is the number of participants receiving at least one unit of intervention.

[2] The per-protocol population is defined in section 5.4

Reasons for non-adherence will be provided.

Appendix D5: Protocol deviations

Protocol deviation	PHBP (N=)	Crystalloid (N=)

Appendix D6: Primary outcome results

The primary outcome is a composite measure consisting of episode mortality and lactate clearance.

Composite outcome, n (%)	PHBP (N=)	Crystalloid (N=)	Relative Risk[1] (95%CI)	p-value

Yes				
No				
Missing				

[1]Output from log-binomial regression model adjusted for IDS. Values of relative risk <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with PHBP.

Composite outcome, n (%)	PHBP (N=)	Crystalloid (N=)	Absolute Risk Difference[1] (95%CI)	p-value
Yes				
No				
Missing				

[1]Output from a binomial regression model with an identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with PHBP.

Appendix D6a: Qualifying event for primary outcome

Qualifying Event for Primary Outcome	PHBP (N=)	Crystalloid (N=)	Total (N=)
Both episode mortality and failure to clear lactate	n (%)	n (%)	n (%)
Episode mortality alone	n (%)	n (%)	n (%)
Failure to clear lactate alone	n (%)	n (%)	n (%)
Missing/Not available	n (%)	n (%)	n (%)

Appendix D7: Secondary outcomes results

Outcome	Time-point	PHBP (N=)	Crystalloid (N=)	Adjusted treatment effect and 95%CI	p-value
Episode Mortality[1]	Up to discharge from acute care	n/N (%)	n/N (%)	Relative risk (95% CI)[2]	p-value
Episode Mortality[1]	Up to discharge from acute care	n/N (%)	n/N (%)	Absolute risk difference (95% CI)[3]	
Failure to achieve lactate clearance[4]	2 hours post-randomisation	n/N (%)	n/N (%)	Relative risk (95% CI)[5]	p-value
Failure to achieve lactate clearance[4]	2 hours post-randomisation	n/N (%)	n/N (%)	Absolute risk difference (95% CI)[6]	
All-cause mortality	Within 3 hours of randomisation	n/N (%)	n/N (%)	Relative risk (95% CI)[7]	p-value
All-cause mortality	Within 3 hours of randomisation	n/N (%)	n/N (%)	Absolute risk difference (95% CI)[8]	
All-cause mortality	Within 3 hours of randomisation[9]	n/N (%)	n/N (%)	Relative risk (95% CI)[7]	p-value
All-cause mortality	Within 3 hours of randomisation[9]	n/N (%)	n/N (%)	Absolute risk difference (95% CI)[8]	
All-cause mortality	Within 30 days of randomisation	n/N (%)	n/N (%)	Relative risk (95% CI)[7]	p-value
All-cause mortality	Within 30 days of randomisation	n/N (%)	n/N (%)	Absolute risk difference (95% CI)[8]	
Pre-hospital time	Time to ED arrival from 999 call	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[10]	p-value
Pre-hospital time	Time to ED arrival from randomisation	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[10]	p-value
Pre-hospital fluid type and volume					
Type & Total volume of Fluids given prior to intervention	Prior to intervention up to ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[11]	p-value
Type & Total volume of Fluids given post intervention	Post intervention up to ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[11]	p-value
Vital Signs					
Systolic blood pressure	On-scene, ED arrival, 2, 6, 12, 24 hours after ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[12]	p-value
Diastolic blood pressure	On-scene, ED arrival, 2, 6, 12, 24 hours after ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[12]	p-value
Heart rate	On-scene, ED arrival, 2, 6, 12, 24 hours after ED	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[13]	p-value

	arrival				
Capillary Oxygen Saturation	On-scene, ED arrival, 2, 6, 12, 24 hours after ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[14]	p-value
Respiratory rate	On-scene, ED arrival, 2, 6, 12, 24 hours after ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[15]	p-value
Other					
Venous/arterial lactate concentration	2 hours after randomisation, ED arrival, 2 hours after ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[16]	p-value
Trauma-induced coagulopathy (INR>1.5)	ED arrival, 2, 6 hours after arrival at ED	n/N (%)	n/N (%)	Relative risk (95% CI)[17]	p-value
Haemoglobin concentration	ED arrival	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[18]	p-value
Cumulative total blood product receipt	6, 12 and 24 hours after arrival at ED	Mean (SD)	Mean (SD)	Mean difference (95% CI)[11]	p-value
ARDS	Within 7 days after ED admission	n/N (%)	n/N (%)	Relative risk (95% CI)[19]	p-value
Transfusion-related complications	24 hours after arrival at ED	n/N (%)	n/N (%)	Relative risk (95% CI)[20]	p-value
Organ Failure Free Days (OFFS)	Up to day 30	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[21]	p-value
ROTEM					
EXTEM					
A05 (mm)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[22]	p-value
CFT (seconds)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[23]	p-value
MCF (mm)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[24]	p-value
CT (seconds)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[25]	p-value
a angle (degree)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[26]	p-value
Ly30 (%)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[27]	p-value
Ly60 (%)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[28]	p-value
FIBTEM					
A05 (mm)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[22]	p-value
CFT (seconds)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[23]	p-value
MCF (mm)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[24]	p-value
CT (seconds)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[25]	p-value
a angle (degree)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[26]	p-value
Ly30 (%)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[27]	p-value

Ly60 (%)	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[28]	p-value
Multiplate (Area under Curve)					
TRAP	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[29]	p-value
ADP	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[29]	p-value
ASPI	First blood sample taken in hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[29]	p-value
Exploratory					
ITU length of stay	Up to discharge from ITU	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[30]	
Hospital length of stay	Up to discharge from hospital	(N ..) Mean (SD)	(N ..) Mean (SD)	Mean difference (95% CI)[30]	
Any Organ Failure by system (SOFA i?3)					
Respiratory	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Neurological	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Cardiovascular	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Liver	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Coagulation	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Renal	During hospital stay (up to day 30)	n/N (%)	n/N (%)	Relative risk (95% CI)[31]	
Use of tranexamic acid	2, 6, 12 and 24 hours after arrival at ED	n/N (%)	n/N (%)	Relative risk (95% CI)[32]	
Surgery	2, 6, 12 and 24 hours after arrival at ED	n/N (%)	n/N (%)	Relative risk (95% CI)[33]	

[1]mortality between time of injury/recruitment and discharge from the primary receiving facility to non-acute care
[2]Relative risk < 1 indicates fewer episode mortality events with PHBP
[3]Absolute risk difference < 0 indicates fewer episode mortality events with PHBP
[4]a failure to achieve lactate clearance ≥20% per hour in the first 2 hours after randomisation
[5]Relative risk < 1 indicates fewer lactate clearance failures with PHBP
[6]Absolute risk difference < 0 indicates fewer lactate clearance failures with PHBP
[7]Relative risk < 1 indicates fewer mortality events with PHBP
[8]Absolute risk difference < 0 indicates fewer mortality events with PHBP
[9]Based only on participants providing an exact time of death.
[10]Difference < 0 indicates shorter time from 999 call or randomisation to ED arrival with PHBP.
[11]Difference < 0 indicates less fluid administered with PHBP.
[12]Difference > 0 indicates higher blood pressure with PHBP.
[13]Difference > 0 indicates higher heart rate with PHBP.
[14]Difference > 0 indicates higher capillary oxygen saturation with PHBP.
[15]Difference > 0 indicates higher respiratory rate with PHBP.
[16]Difference < 0 indicates lower venous lactate concentration with PHBP.
[17]Relative risk < 1 indicates lower rate of trauma-induced coagulopathy with PHBP
[18]Difference < 0 indicates lower haemoglobin concentration with PHBP.
[19]Relative risk < 1 indicates lower rate of ARDS with PHBP
[20] Relative risk < 1 indicates lower rate of transfusion-related complications with PHBP.
[21]Difference > 0 indicates higher number of days free from organ failure with PHBP

[22] Difference > 0 indicates higher amplitude after 5 minutes with PHBP.
[23]Difference < 0 indicates lower clot formation time with PHBP.
[24]Difference > 0 indicates higher maximum clot firmness with PHBP.
[25]Difference < 0 indicates lower coagulation time with PHBP.
[26]Difference < 0 indicates lower speed of clot formation time with PHBP.
[27]Difference < 0 indicates lower lysis index at 30 minutes with PHBP.
[28]Difference < 0 indicates lower lysis index at 60 minutes with PHBP.
[29]Difference > 0 indicates higher agonist AUC with PHBP.
[30]Difference > 0 indicates longer length of stay with PHBP.
[31]Relative risk < 1 indicates fewer organ failure events with PHBP.
[32]Relative risk < 1 indicates lower rate of tranexamic acid use with PHBP.
[33]Relative risk < 1 indicates lower rate of surgery with PHBP.

Appendix D8: Safety

	PHBP (N=)	Crystalloid (N=)	p-value
Transfusion-related lung injury	n (%)	n (%)	p-value
Any thromboembolism	n (%)	n (%)	p-value
Deep-vein thrombosis	n (%)	n (%)	p-value
Pulmonary embolism	n (%)	n (%)	p-value
Stroke	n (%)	n (%)	p-value
Other	n (%)	n (%)	p-value
Infection (suspicion, or clinical evidence of)	n (%)	n (%)	p-value
Intra-abdominal	n (%)	n (%)	p-value
Meningitis	n (%)	n (%)	p-value
Respiratory	n (%)	n (%)	p-value
UTI	n (%)	n (%)	p-value
Soft tissue	n (%)	n (%)	p-value
Indwelling device	n (%)	n (%)	p-value
Blood-born	n (%)	n (%)	p-value
Other	n (%)	n (%)	p-value

	PHBP (N=)	Crystalloid (N=)	p-value
Total number of SAEs	n	n	
Total number of participants experiencing an SAE	n (%)	n (%)	<insert p-value>
Total number of SUSARs	n	N	
Total number of participants experiencing an SUSAR	n (%)	n (%)	<insert p-value>

A line by line listing of each SAE may be appropriate for some studies and can be included in an Appendix to the main report; the table below provides a guide for how the line listing of SAE data could be presented.

Summary of SAE	Reason for Reporting	Causality	Action taken
PHBP			
1 <insert description of			

~~SAE>~~			
2			
3			
4			
Crystalloid			
1			
2			
3			
4			

Appendix D9: Subgroup analysis for primary outcome

Subgroup description	PHBP (N=)	Crystalloid (N=)	Adjusted relative risk (95% CI)	p-value for interaction
IDS				
Site 1	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
Site 2	n (%)	n (%)	Relative risk (95% CI)[1]	
Site 3	n (%)	n (%)	Relative risk (95% CI)[1]	
Site 4	n (%)	n (%)	Relative risk (95% CI)[1]	
Mode of transport				
Air	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
Ground	n (%)	n (%)	Relative risk (95% CI)[1]	
Initial Lactate Concentration				

s2.2 mmol/L	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
>2.2 mmol/L	n (%)	n (%)	Relative risk (95% CI)[1]	
Cardiac Arrest				
Yes	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
No	n (%)	n (%)	Relative risk (95% CI)[1]	
Time to ED from injury				
s 1 hour	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
>1 hour	n (%)	n (%)	Relative risk (95% CI)[1]	
Mode of injury				
Blunt	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
Penetrating	n (%)	n (%)	Relative risk (95% CI)[1]	
Crush	n (%)	n (%)	Relative risk (95% CI)[1]	
Volume of pre-hospital fluid given				
4 units	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
< 4 units	n (%)	n (%)	Relative risk (95% CI)[1]	
Age				
<50 years	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
50 - 70 years	n (%)	n (%)	Relative risk (95% CI)[1]	
>70 years	n (%)	n (%)	Relative risk (95% CI)[1]	
Head Injury				
Positive	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
Negative	n (%)	n (%)	Relative risk (95% CI)[1]	
Compressible Haemorrhage				
Compressible Haemorrhage	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
Non-Compressible Haemorrhage	n (%)	n (%)	Relative risk (95% CI)[1]	
Pre-morbid drug history				
Anticoagulant/antiplatelet medication	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
No anticoagulant/antiplatelet medication	n (%)	n (%)	Relative risk (95% CI)[1]	
Age of blood products				
<8 days	n (%)	n (%)	Relative risk (95% CI)[1]	p-value
≥8 days	n (%)	n (%)	Relative risk (95% CI)[1]	

[1]Output from log-binomial regression model. Values of relative risk <1 indicate lower rate of negative events (episode mortality or failure to clear lactate concentration) with PHBP.

Appendix D10: Exploratory Bayesian analysis for primary outcome

The primary outcome is a composite measure consisting of episode mortality and lactate clearance.

PHBP (N=)	Crystalloid (N=)	Median Relative Risk Ratio	95% HDI	Probability of Relative Risk Ratio		
				< 1.0	< 0.8	<0.7

[1]Output from Bayesian log-binomial regression model adjusted for IDS. Values of relative risk <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with PHBP.

PHBP (N=)	Crystalloid (N=)	Median Risk Difference	95% HDI	Probability of Risk Difference		
				< 0%	< -10%	< -20%

[1]Output from Bayesian binomial regression model with an identity link adjusted for IDS. Values of risk difference < 0 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with PHBP.

Appendix D10a: Exploratory Bayesian analysis for episode mortality

PHBP (N=)	Crystalloid (N=)	Median Relative Risk Ratio	95% HDI	Probability of Relative Risk Ratio		
				< 1.0	< 0.8	<0.7

[1]Output from Bayesian log-binomial regression model adjusted for IDS. Values of relative risk <1 indicate fewer events of episode mortality with PHBP.

PHBP (N=)	Crystalloid (N=)	Median Risk Difference	95% HDI	Probability of Risk Difference		
				< 0%	< -10%	< -20%

[1]Output from Bayesian binomial regression model with an identity link adjusted for IDS. Values of risk difference < 0 indicate fewer events of episode mortality with PHBP.

Appendix D10b: Exploratory Bayesian analysis for lactate clearance

PHBP (N=)	Crystalloid (N=)	Median Relative Risk Ratio	95% HDI	Probability of Relative Risk Ratio		
				< 1.0	< 0.8	<0.7

[1]Output from Bayesian log-binomial regression model adjusted for IDS. Values of relative risk <1 indicate fewer failures to clear lactate concentration with PHBP.

PHBP (N=)	Crystalloid (N=)	Median Risk Difference	95% HDI	Probability of Risk Difference		
				< 0%	< -10%	< -20%

[1]Output from Bayesian binomial regression model with an identity link adjusted for IDS. Values of risk difference < 0 indicate fewer failures to clear lactate concentration with PHBP.