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Nicholas Crombie, Heidi A Doughty, Jonathan RB Bishop, Amisha Desai, Emily F Dixon, James M Hancox, Mike J Herbert, Caroline Leech, Simon J Lewis, Mark R Nash, David N Naumann, Karen Piper, Gemma Slinn, Hazel Smith, Iain M Smith, Rebekah K Wale, Alastair Wilson, Aisling Crombie, Mark Midwinter, Natalie Ives and Gavin D Perkins

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Abstract

Resuscitation with pre-hospital blood products in adults with trauma-related haemorrhagic shock: the RePHILL RCT

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Background: The treatment of traumatic haemorrhagic shock has been transformed through better haemorrhage control, use of tranexamic acid and use of blood products. The improved survival seen from these strategies has stimulated an interest in pre-hospital transfusion.

Objectives: To determine if the clinical effectiveness of resuscitation with red blood cells and lyophilised plasma was superior to 0.9% saline for improving tissue perfusion and reducing mortality in adults with haemorrhagic shock following major trauma.

Design: A multi-centre, allocation concealed, open-label, parallel group, randomised controlled trial (with internal pilot).

Setting: The trial was conducted in four civilian pre-hospital critical care services who operated within the National Health Service (NHS) England Major Trauma Networks.

Participants: Adults (aged ≥16 years) who had sustained traumatic injuries, were attended by a pre-hospital emergency medical team and were hypotensive (systolic blood pressure <90 mmHg or absence of radial pulse) as a consequence of traumatic haemorrhage were eligible for inclusion. The exclusion criteria were known or apparently <16 years, blood administered on scene prior to arrival of the RePHILL team, traumatic cardiac arrest where (1) the arrest occurred prior to arrival of

the team and/or (2) the primary cause is not hypovolaemia, refusal of blood product administration, known Jehovah's Witness, pregnancy, isolated head injury without evidence of external haemorrhage, prisoners in the custody of HM Prison and Probation Service.

Interventions: Participants were randomised to receive up to either two units each of red blood cells and lyophilised plasma or up to 1 L 0.9% saline. Treatment was administered through the intravenous or intraosseous route.

Main outcome measures: The primary outcome was a composite of episode mortality and/or impaired lactate clearance. The secondary outcomes included the individual components of the primary outcome.

Results: From 6 December 2016 to 2 January 2021, pre-hospital medical teams randomised 432 participants to red blood cell/lyophilised plasma (n = 209) or 0.9% saline (n = 223) out of a target sample size of 490. Most participants were white (62%), males (82%), median age 38 (interquartile range 26 to 58), involved in a road traffic collision (62%) with severe injuries (median injury severity score 36, interquartile range 25 to 50). Prior to randomisation participants had received on average 430 ml crystalloid fluids and tranexamic acid (90%). The primary outcome occurred in 128/199 (64.3%) of participants randomised to red blood cell/lyophilised plasma and 136/210 (64.8%) randomised to 0.9% saline [adjusted risk difference −0.025% (95% confidence interval −9.0% to 9.0%), p = 0.996]. The event rates for the individual components of the primary outcome, episode mortality and lactate clearance were not statistically different between groups [adjusted average differences −3% (−12% to 7%); p = 0.57 and −5% (−14% to 5%), p = 0.33, respectively].

Limitations: Recruitment stopped prematurely due to disruption caused by the COVID-19 pandemic.

Future work: Identify the characteristics of patients who may benefit from pre-hospital blood products and whether alternative transfusion regimens are superior to standard care.

Conclusions: The trial did not demonstrate that pre-hospital red blood cell/lyophilised plasma resuscitation was superior to 0.9% saline for trauma-related haemorrhagic shock.

Trial registration: This trial is registered as ISRCTN62326938.

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Report Supplementary Material 1 Statistical analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/TDNB9214).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

CI	confidence interval	PHEM	pre-hospital emergency medicine
CONSORT	Consolidated Standards of Reporting Trials	PI	principal investigator
DMEC	Data Monitoring and Ethics Committee	PPI	patient and public involvement
ED	emergency department	RBC	red blood cells
IDS	intervention delivery site	RCT	randomised controlled trial
INR	international normalised ratio	SBP	systolic blood pressure
IQR	interquartile range	SD	standard deviation
LyoPlas	lyophilised plasma	TAAS	The Air Ambulance Service
PHBP	pre-hospital blood products	TSC	Trial Steering Committee

Plain language summary

Blood and plasma are life-saving treatments for people with severe bleeding following major traumatic injury. Until recently, they could only be administered in hospital. The Resuscitation with Pre-Hospital Blood Products (RePHILL) trial tested whether providing these treatments before the injured person arrives in hospital was better than current NHS treatment (a clear fluid called 0.9% saline).

We worked with NHS ambulance services, air ambulance charities, blood transfusion laboratories, blood bikers and the NHS major trauma networks to make blood and plasma available to patients outside the hospital. Blood banks prepared sealed boxes according to a schedule prepared by the research team. Half the boxes contained blood and plasma (treatment) and half contained salty water (control). The pre-hospital critical care teams did not know what was in the sealed boxes.

Critical care doctors and paramedics assessed people who had sustained major traumatic injuries. People with severe bleeding and a critically low blood pressure were recruited into the trial. The critical care team opened the sealed box and administered the contents of the box (blood/plasma or saline). The trial compared how effective the treatments were by looking at a combined outcome comprising (1) how quickly the body cleared a waste product called lactate and (2) whether the individual died.

Four hundred and thirty-two people participated in the trial, slightly less than the 490 planned due to the trial being interrupted by COVID-19. Two hundred and nine people were in the blood/plasma group and 223 in the 0.9% saline group. The combined outcome of lactate clearance and mortality was very similar between the two groups occurring in around 6 out of 10 people in each group.

Further research is required to work out who might benefit from pre-hospital blood/plasma and how best to measure that benefit in future trials.

Scientific summary

Background

For many years, trauma care focused upon providing basic treatments on scene to facilitate safe transfer to hospital for further and definitive care. In the last two decades however, the emphasis in civilian practice has started to change in the direction of delivering more advanced interventions to patients while still in the pre-hospital phase. This shift, intended to provide earlier physiological stability and prevent so-called secondary damage occurring, has been driven in part by lessons learned in conflict by military medical systems, and include advanced haemorrhage control and blood product-based resuscitation.

The introduction of blood component resuscitation during military casualty retrieval initially produced encouraging results with reports of reduced mortality amongst recipients receiving red blood cells (RBCs) and pre-thawed plasma. Extrapolating results from military trauma-based studies into civilian practice is not straightforward. The mechanisms and severity of injury sustained in conflict are rarely replicated in civilian practice, the patient demographic of active combatants is comparatively narrow and the medical infrastructure in dedicated field hospitals is different to many civilian emergency departments (EDs).

The provision of blood products as early treatment of major haemorrhage may seem logical, but it is also not without complication. Stored RBCs carry a significant metabolic burden when administered rapidly and have the potential to cause further disruption to coagulation and myocardial function. There are also considerations around the provision of blood products including the demand for 'universal' blood products, regulatory compliance and secure cold-chain governance to avoid unnecessary wastage of products.

The lack of robust evidence surrounding the administration of pre-hospital RBCs or plasma in civilian practice, coupled with the challenges this poses to the transfusion community, made a prospective randomised controlled trial (RCT) important if further developments in this area of practice are to be justifiable.

Objectives

The primary objective of the RePHILL trial was to investigate the clinical effectiveness of pre-hospital blood products (PHBP) resuscitation compared to the current standard care of restricted crystalloid-based resuscitation in participants developing haemorrhagic shock following major trauma. This was assessed through the primary outcome, a composite of episode mortality and a failure to clear lactate.

The secondary objectives included examining the effect of PHBP on systolic blood pressure (SBP), heart rate, capillary oxygen saturation, on scene times, fluid and transfusion requirements, coagulopathy and platelet function, transfusion-related complications, blood product wastage and haemoglobin concentration on ED arrival.

Methods

Ethics and regulatory approvals

The study was sponsored by University Hospitals Birmingham NHS Foundation Trust and approved by the South Central Research Ethics Committee (15/SC/0691) and the Medicines and Healthcare products

Regulatory Agency. The EudraCT number is 2015-001401-13 and International Standard Randomised Controlled Trial number is ISRCTN62326938. The trial was co-ordinated by Birmingham Clinical Trials Unit.

Design

The study was a multi-centre, allocation concealed, open-label, parallel group, RCT.

Inclusion and exclusion criteria

Participants were eligible for inclusion if the following criteria were met:

- traumatic injury;
- pre-hospital emergency medical (PHEM) team attend;
- hypotension SBP <90 mmHg (or absence of palpable radial pulse) believed to be due to traumatic haemorrhage.

The trial exclusion criteria were:

- children (known or apparently aged <16 years);
- blood administered on scene, prior to randomisation;
- traumatic cardiac arrest where (1) the arrest occurred prior to arrival of the PHEM team and/or (2) the primary cause is not hypovolaemia;
- 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 and Probation Services.

Setting

The trial was conducted in four civilian pre-hospital critical care services who operated within the NHS England major trauma networks.

- East Anglian Air Ambulance, Norwich, UK (www.eaaa.org.uk, accessed 7 February 2022).
- Magpas Air Ambulance, Huntingdon, UK (www.magpas.org.uk, accessed 7 February 2022).
- Midlands Air Ambulance and MERIT, West Midlands Ambulance Service NHS Trust, West Midlands, UK (www.midlandsairambulance.com and https://wmas.nhs.uk, accessed 7 February 2022).
- The Air Ambulance Service, Warwickshire (https://theairambulanceservice.org.uk, accessed 7 February 2022).

Major trauma network treatment protocols were informed by the National Institute for Health and Care Excellence Clinical Guidelines 39 Major trauma: assessment and initial management (www.nice.org.uk/guidance/ng39, accessed 7 February 2022).

Consent

Major traumatic haemorrhage is a life-threatening condition that requires urgent treatment. The time-critical nature meant that it was impractical to obtain informed consent from the patient, a personal or professional legal representative without the potential for causing harm through delaying treatment. In accordance with the Medicines for Human Use (Clinical Trials; Amendment No. 2) Regulations 2006, approval was obtained from the Research Ethics Committee to enrol patients prior to obtaining informed consent. For patients who survived to be admitted to hospital, the local research teams sought written, informed consent from the patient or a legal representative to continue in the trial.

Randomisation and masking

Randomisation (variable block size, stratified by site 1 : 1 ratio) was implemented through a central and secure trial database at the Birmingham Clinical Trials Unit. Blood bank staff prepared sealed treatment

boxes with either red blood cell/lyophilised plasma (LyoPlas) or 0.9% saline according to the randomisation schedule.

Allocation concealment was implemented by using opaque boxes that were externally identical in appearance and weight. This ensured pre-hospital teams were unaware of the treatment allocation prior to enrolling a participant.

When a participant met the trial eligibility criteria, randomisation was achieved by opening the sealed boxes. Once opened, those administering the trial intervention were aware of group assignment. Those assessing outcomes in hospital were not informed of group assignment but may have been able to access it through hospital records.

Trial treatments

- Intervention: Up to two units of RBC and up to two units of LyoPlas.
- Control: Up to four (250 ml) bags of 0.9% saline.

Trial treatments were administered until either hospital arrival or until hypotension resolved (i.e. SBP ≥90 mmHg or a radial pulse was palpable). If all four units of trial treatments were given, non-trial 0.9% saline was then given. Following arrival in hospital, further resuscitation and transfusion was at the discretion of the treating clinician.

The primary outcome was a composite measure consisting of episode mortality and lactate clearance defined as a failure to achieve lactate clearance ≥20% per hour in the first 2 hours from randomisation.

The secondary outcomes comprised:

- 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 (SBP, heart rate, capillary oxygen saturation);
- (venous) lactate concentration;
- haemoglobin concentration on ED arrival;
- trauma-induced coagulopathy [defined as International Normalised Ratio (INR) >1.5];
- coagulation measured viscoelastically by rotational thromboelastometry (ROTEM);
- platelet function using multiple electrode impedance aggregometry (MultiPlate);
- total blood product receipt;
- acute respiratory distress syndrome;
- transfusion-related complications;
- organ failure-free day.

Sample size and statistical analysis

The trial set out to detect a 10% absolute difference between groups in the proportion of participants experiencing the primary outcome assuming an event rate of 20% in the control group and 10% in the intervention. For 80% power and type 1 error rate of 0.05, 438 participants (219 per group) were required. Allowing for 10% attrition, the sample size was set at 490 participants.

During May 2018, the Data Monitoring Committee (DMC) reported a much higher than anticipated pooled event rate for the primary outcome (65%) to the Trial Steering Committee (TSC). The TSC advised to continue the trial with the original sample size unchanged, noting that the trial retained 80% power to detect a relative risk of 0.82 (71.7% control, 58.3% intervention).

All primary analyses of the primary and secondary outcomes followed the intention-to-treat principle. The analyses used a model-based approach with pre-hospital critical care service included as a fixed

effect covariate in the model. Treatment effects are presented with two-sided 95% confidence intervals (CIs). No adjustment for multiple comparisons was made. Binary outcomes were analysed using log-binomial regression models to obtain adjusted relative risks along with 95% CIs. A relative risk <1 favoured the RBC/LyoPlas group. Adjusted risk differences along with 95% CIs were estimated using a binomial regression model with identity link. A risk difference <0 favoured the RBC/LyoPlas group. Continuous data were analysed using linear regression models to obtain adjusted mean differences between groups along with 95% CIs. We planned a priori a Bayesian analysis of the primary outcome and its individual components using non-informative, sceptical and informative priors.

Patient and public involvement

Patient and public involvement (PPI) was intrinsic to the development, management and oversight of RePHILL.

During the initial stages of the trial's development the sponsor engaged a major trauma-specific focus group, the purpose being for PPI representatives to provide their perspective on the study, ask questions and discuss challenges. Valuable feedback was provided from this session that helped drive how key issues (e.g. patient consent) were addressed in the trial protocol. Furthermore, given the nature of the trial interventions, the Jehovah's Witness Hospital Liaison Committee were also consulted and provided guidance on the management of patients within the Witness community.

Throughout the life of the trial, dedicated representatives who sat on both the Trial Management Group (TMG) and TSC provided PPI input.

Results

Recruitment

The trial opened to recruitment on 29 November 2016, with the first patient being recruited on 6 December 2016. The last patient was recruited on 1 January 2021. The trial was closed on 2 January 2021 prior to achieving the intended sample size due to the ongoing impact of the COVID-19 pandemic. The decision to close the trial was made by the TSC and sponsor, without any knowledge of the data or results of interim analyses.

Five hundred and eighty potential participants were assessed for eligibility from which 432 participants were randomised [RBC/LyoPlas (n = 209) or control (n = 223)].

Baseline characteristics

The baseline characteristics were well-balanced between the two groups. Participants were predominantly white (62%), males (82%). The median age was 38 [interquartile range (IQR) 26 to 58]. Road traffic collision (62%), stabbing (16%) and falls (14%) were the commonest mechanisms of injury. Injury patterns were blunt trauma (79%) and penetrating trauma (22%). Brain injury was also present in 48%. Participants received on average 430 ml crystalloid fluids and tranexamic acid (90%) prior to randomisation.

Participants were severely injured. The median injury severity score was 36 (IQR 25 to 50); median new injury severity score was 43 (IQR 34 to 57) and average blood pressure was 73/46 mmHg. Transfer to hospital was facilitated by road ambulance in 62% of participants. The median transfer time was 83 (IQR 65 to 100.5) minutes after the emergency call.

Intervention delivery and follow-up

199/209 randomised to the intervention group (RBC/LyoPlas) received the allocated intervention. The average (mean) volume of fluid administered was 1.57 [standard deviation (SD) 443 ml] units of RBC and 1.25 units LyoPlas (SD 709 ml). Five participants were withdrawn from follow-up.

215/233 randomised to the control group (0.9% saline) received the allocated intervention. The average volume infused was 2.55 units of 0.9% saline (638 ml).

Primary outcome

Amongst the participants randomised to RBC/LyoPlas, 128/199 (64.3%) experienced the primary outcome compared to 136/210 (64.8%) of those randomised to 0.9% saline. The adjusted risk ratio was 1.01 (95% CI 0.88 to 1.17) and adjusted difference −0.025% (95% CI −9.0% to 9.0%), $p = 0.996$.

The breakdown for the composite primary outcome for the RBC/LyoPlas group was:

- Failure to clear lactate alone [$n = 40$ (20%)].
- Failure to clear lactate and mortality [$n = 58$ (29%)].
- Mortality alone [$n = 30$ (15%)].

The breakdown for the composite primary outcome for the 0.9% saline group was:

- Failure to clear lactate alone [$n = 37$ (18%)].
- Failure to clear lactate and mortality [$n = 76$ (36%)].
- Mortality alone [$n = 23$ (11%)].

The Bayesian analysis revealed that the probability that the risk difference for the primary outcome was >0% or >10% was 48.2% and 1.3% (non-informative priors), 44.1% and 0.3% (sceptical priors) and 53.4% and 1.6% (informative priors) respectively.

Secondary outcomes

The event rates for the individual components of the primary outcome comprised of:

- Episode mortality 88/203 (43%) in the RBC/LyoPlas group compared to 99/218 (45%) in the 0.9% saline group [adjusted average differences −3% (−12% to 7%), $p = 0.57$].
- Failure to clear lactate 98/196 (50%) compared to 113/206 (55%) [adjusted average difference −5% (−14% to 5%), $p = 0.33$].

Vital signs on arrival at hospital and through to 24 hours were similar between groups.

The haemoglobin concentration on arrival to hospital was 133 (19) g/L in the RBC/LyoPlas group compared to 118 (23) g/L in the 0.9% saline group, an adjusted average difference of 15 g/L (95% CI 10 to 19), $P < 0.0001$. There were no between group differences in tests of coagulation, and platelet function was similar.

Blood product use was similar following hospital admission through to 24 hours. A post-hoc analysis found that total (pre-hospital and hospital) blood and plasma use was higher in the RBC/LyoPlas group [mean difference 1.80 units (95% CI 0.58 to 3.01) and 1.54 units (95% CI 0.57 to 2.50)] respectively.

Death within 3 hours occurred in 32/197 (16%) compared to 46/208 (22%), adjusted average difference −7% (−15% to 1%); $P = 0.08$, and within 30 days it occurred in 86/204 (42%) compared to 99/219 (45%), adjusted average difference −4% (−13% to 6%); $P = 0.44$.

Adverse events

Rates of complications and adverse events were similar across groups, and only two serious adverse events were recorded.

Complications relating to transfusion in the first 24 hours were similar for the RBC/LyoPlas group 11/148 (7%); compared to 0.9% saline 9/137 (7%).

Acute respiratory distress syndrome developed amongst 9/142 (6%) in the RBC/LyoPlas group and 3/129 (2%) in the 0.9% saline group [adjusted relative risk 2.71 (0.75 to 9.81)].

The number of organ failure-free days were also similar across groups [12.9 (SD 13.0) RBC/LyoPlas vs. 12.1 (13.1) 0.9% saline].

No patients required dose reductions or had treatment discontinued for drug-related toxicity. There were no treatment-related deaths.

Conclusion

In adults with severe injuries and haemorrhagic shock secondary to major trauma in a civilian setting, the RePHILL trial did not demonstrate that pre-hospital RBC/LyoPlas resuscitation was superior to 0.9% sodium chloride.

Future research should seek to identify if specific groups of patients may benefit and explore the effects of alternative transfusion strategies.

Trial registration

This trial is registered as ISRCTN62326938.

Funding

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Chapter 1 Introduction

Background

For many years, trauma care has been predominantly based upon offering casualties with traumatic injuries basic treatment on scene to then safely allow transfer to hospital for further and definitive care. In the last two decades however, the emphasis in civilian practice has started to change in the direction of delivering more advanced interventions to patients while still in the pre-hospital phase. This shift, intended to provide earlier physiological stability and prevent so-called secondary damage occurring, has been driven in part by lessons learned in conflict by military medical systems, and includes advanced haemorrhage control and blood product-based resuscitation.[1–3]

The introduction of blood component resuscitation during military casualty retrieval initially produced encouraging results with reports of reduced mortality amongst recipients receiving red blood cells (RBCs) and pre-thawed plasma.[4–6] However, a subsequent systematic review and meta-analysis of studies investigating outcomes following pre-hospital transfusion across both military and civilian practice found only modest advantages in those with moderate severity of injury.[7] In more recent years, two large randomised trials examining the use of pre-hospital plasma produced differing results – one trial favoured the use of plasma[8] and one trial was stopped early due to futility.[9] There is therefore a lack of consistent and reliable data, confounded by the wide variety of systems in which studies have been conducted. In 2020, a review of pre-hospital transfusion of RBCs was unable to demonstrate a survival benefit, again highlighted the absence of randomised controlled trials (RCTs) and recommended further studies incorporating the use of individualised transfusion criteria and the use of plasma.[10]

Extrapolating results from military trauma-based studies into civilian practice is not straightforward. The mechanisms and severity of injury sustained in conflict are rarely replicated in civilian practice, the patient demographic of active combatants is comparatively narrow and the medical infrastructure in dedicated field hospitals is different to many civilian emergency departments (EDs).

The provision of blood products as early treatment of major haemorrhage may seem logical, but it is also not without complication. Stored citrated blood can present a significant metabolic burden when administered rapidly and has the potential to cause further disruption to coagulation and myocardial function, especially in trauma.[11] There are also considerations around the provision of blood products including the demand for 'universal' blood products, regulatory compliance and secure cold-chain governance to avoid unnecessary wastage of products.[12]

The lack of robust evidence surrounding the administration of pre-hospital RBCs or plasma in civilian practice, coupled with the challenges this poses to the transfusion community, make a prospective RCT important if further developments in this area of practice are to be justifiable.[13]

We present the results of resuscitation with pre-hospital blood products (PHBP) (RePHILL) – a prospective multi-centre RCT which investigates the hypothesis that the administration of pre-hospital RBCs and lyophilised plasma (LyoPlas) would improve tissue perfusion as measured by the clearance of lactate and/or reduce mortality in patients demonstrating shock secondary to traumatic haemorrhage compared to resuscitation with crystalloid infusion.[14]

Chapter 2 Methods

Study design

We conducted a multi-centred two-arm (1 : 1) open-labelled phase 3 RCT of pre-hospital blood product administration versus standard care for patients following traumatic haemorrhage. Research Ethics Committee approval was granted prior to study initiation (South Central – Oxford C, ref: 15/SC/0691). The trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN62326938) as well as with the European Union Drug Regulating Authorities Clinical Trials Database (registration: 2015-001401-13) and the Medicines and Healthcare products Regulatory Agency (Clinical Trials Authorisation: 16719/0228/001-0001). The trial was run in accordance with Good Clinical Practice requirements. Reporting is undertaken according to the Consolidated Standards of Reporting Trials (CONSORT) guidance.[15] A trial protocol has been published previously.[14] *Figure 1* presents a summary of the trial protocol.

Internal pilot

The RePHILL trial included an internal pilot. The purpose of the internal pilot was to assess the trial logistics to determine if it is both feasible and practical to carry on and recruit into the trial. It was intended that the pilot would be run at multiple sites to validate the multi-centre aspects of the trial.

The trial progression criteria were defined as:

- minimum of 25 participants recruited across at least two active sites;
- in participants recruited to the trial intervention arm, at least one unit of RBC 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.

Changes to trial protocol

There were no major changes made to the study design. *Table 1* lists the key amendments to the trial protocol.

Eligibility criteria

Eligibility was assessed by the Pre-Hospital Emergency Medical (PHEM) team (doctor and/or paramedic). The principal investigator (PI) for intervention delivery sites (IDS) was always a medically qualified doctor, and they were responsible for maintaining oversight of the confirmation of eligibility process.

Inclusion criteria

Patients were eligible for inclusion in RePHILL if:

- they had suffered a **traumatic injury;**
- the PHEM team attended;
- **hypotension** [systolic blood pressure (SBP) <90 mmHg or absence of palpable radial pulse] believed to be due to traumatic haemorrhage.

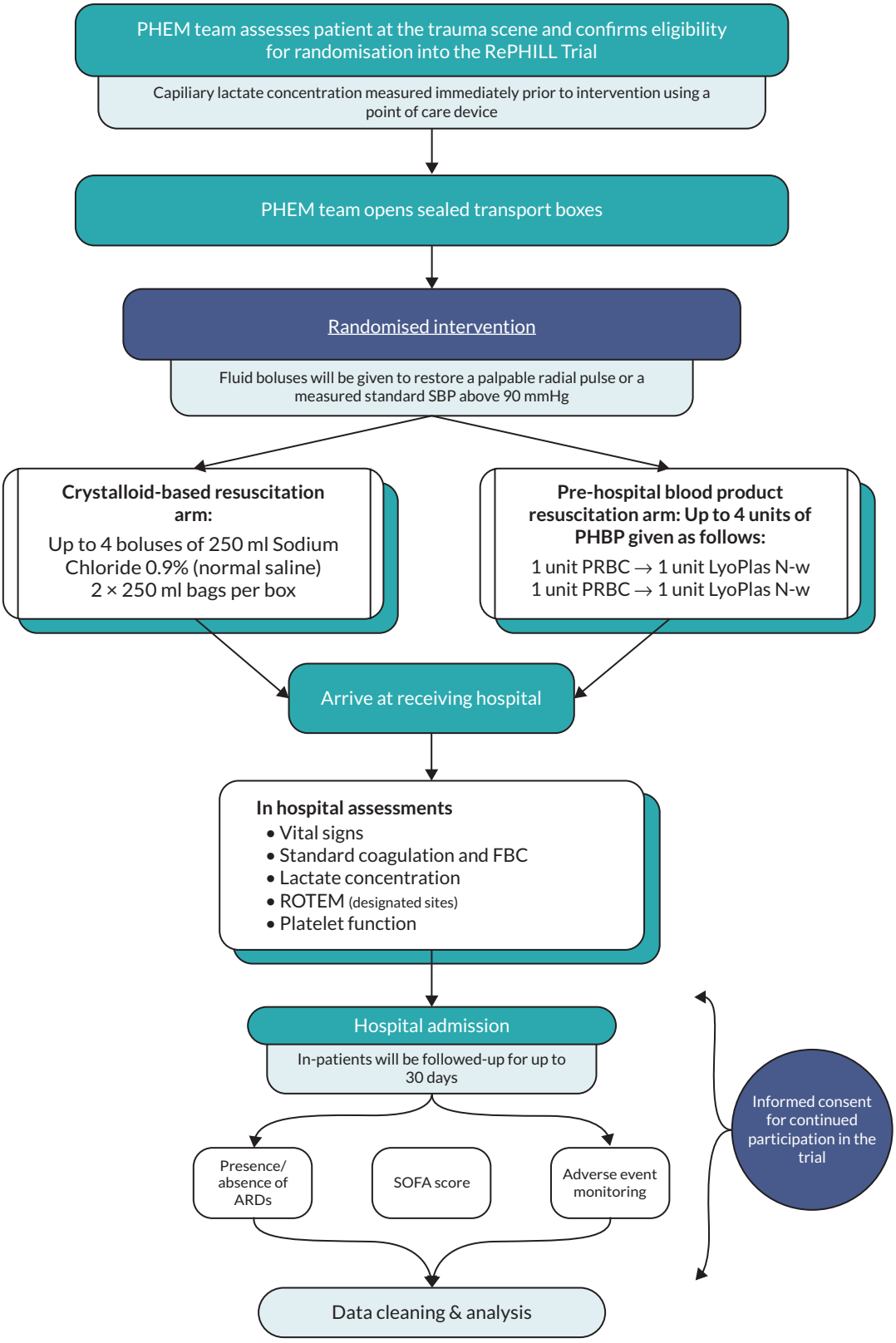

FIGURE 1 RePHILL trial protocol summary.

TABLE 1 Key amendments to the trial protocol

Amendment date	Protocol version number	Summary of amendment
18 July 2016	1.1	Changes to the chief and PIs Addition of new sites
21 September 2016	1.1	Change of PI
	2.0	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 (see note 1) Update to exclusion criteria (see note 2) 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 on adverse event (AE) reporting Clarification on data collection Statistical updates Clarification on monitoring requirements Removal of participating sites Change of PIs
6 February 2017 to 1 February 2019 (covering 11 amendments)	2.0	Change of PIs and addition of sites
18 February 2019	3.0	Removal of participating sites table RePHILL Trial Protocol version 3.0, 8 April 2019 EudraCT Number: 2015-001401-13 Page 4 of 58 Update to secondary outcomes (see note 3) Update to who will assess and confirm eligibility (see note 4) Update to the exclusion criteria (see note 2) Removal of NHS digital, long-term follow-up Clarification to trial procedures on scene Clarification of informed consent procedure Update on blood sampling Removal of blood sampling for future analysis Update to pharmacovigilance reporting requirements Update to categorisation of causality table Update to data protection regulations Update to end of trial definition

TMG, Trial Management Group
Note 1: It was clarified that episode mortality refers to mortality between time of injury/recruitment and discharge from the primary receiving facility to non-acute care, that is discharge home or to long-term care, to rehabilitation or repatriation to a hospital closer to their normal residence.
Note 2: The trial exclusion criteria were revised so that the following groups of participants were ineligible: traumatic cardiac arrest where (1) the arrest occurred prior to arrival of the PHEM team and/or (2) the primary cause is not hypovolaemia; blood administered on scene prior to arrival of the RePHILL PHEM team; isolated head injury without evidence of external haemorrhage; known prisoners in the custody of HM Prison and Probation Service.
Note 3: Changes to the secondary outcomes included the addition of all-cause mortality within 30 days of randomisation; haemoglobin at hospital admission; and vital signs at 12 hours after ED arrival.
Note 4: Eligibility assessment was extended to include RePHILL-trained paramedics in addition to doctors.

Exclusion criteria

Patients were excluded if:

- children (known or apparently aged <16 years);
- blood administered on scene, prior to arrival of the RePHILL PHEM team;
- traumatic cardiac arrest where (1) the arrest occurred prior to arrival of the PHEM team and/or (2) the primary cause is not hypovolaemia;

- 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 and Probation Service.

Clinician training

All clinical staff who participated in the trial completed online Good Clinical Practice and protocol training. At the start of the trial, authorisation for the administration of the interventions was limited to doctors working with the PHEM teams. However, this led to missed recruitments by paramedic-only crews. With agreement from relevant parties, the protocol was amended in 2019 and developed a training programme to ensure the safe administration of blood products by paramedics in the context of the trial, that is non-medical authorisation (NMA).

A bespoke training to enable NMA of blood was developed. The training programme comprised four elements as outlined in *Figure 2*. The programme was successful delivered to three critical care paramedics who cascaded the training to 14 colleagues.

Informed consent

Prospective informed consent for the participation in the trial was not feasible due to the nature of the injuries and incapacitation that was anticipated to fulfil eligibility criteria. Patients were enrolled in the trial in accordance with Good Clinical Practice, the Declaration of Helsinki, the Clinical Trials Regulations 2004 and the Human Tissue Act 2004. After enrolment, consent for participants to remain in the trial was sought as early as feasible and appropriate when capacity was regained. At the time of enrolment, consent was sought from a professional legal representative shortly after arrival at the receiving

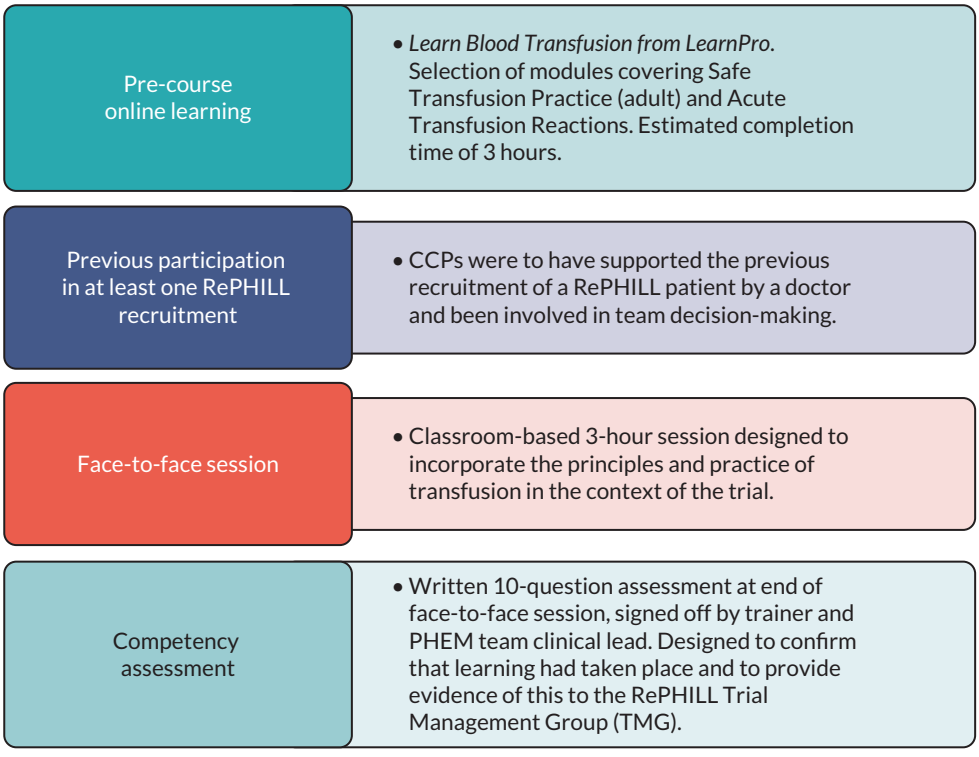

FIGURE 2 Non-medical authorisation programme.

hospital. Further consent was sought from a personal or legal representative (such as a close relative or friend). Information regarding the trial was on display in locations likely to be visited by relatives, with a brief summary of the trial and contact details for further information. Some patients may wish to avoid blood product transfusion due to prior held beliefs (such as the Jehovah's Witness community). In such circumstances, an advance medical directive would have been sought (as per usual practice in emergency resuscitation).

Although an eligibility criterion was that participants should be aged 16 or over, due to the nature of the trial it was not always possible to confirm the age of the participant before recruitment. If a participant was recruited and later found to be under the age of 16, child assent was sought alongside consent from a parent or guardian.

Study setting

The trial was situated within NHS England major trauma network. PHEM teams were recruited to become IDS. At the start of the research, it was anticipated recruitment would take place in six regional air ambulances services. During the set-up of the trial, two air ambulance services withdrew (Dorset and Somerset Air Ambulance and Essex and Herts Air Ambulance) due to loss of equipoise. A further air ambulance service briefly joined the trial (Yorkshire Air Ambulance) but subsequently withdrew prior to recruitment starting due to loss of equipoise.

The following air ambulances participated in the trial:

- East Anglian Air Ambulance, Norwich, UK (www.eaaa.org.uk, accessed 7 February 2022)
- Magpas Air Ambulance, Huntingdon, UK (www.magpas.org.uk, accessed 7 February 2022)
- Midlands Air Ambulance and MERIT, West Midlands Ambulance Service NHS Trust, West Midlands, UK (www.midlandsairambulance.com and https://wmas.nhs.uk, accessed 7 February 2022)
- The Air Ambulance Service, Warwickshire (https://theairambulanceservice.org.uk, accessed 7 February 2022)

The hospital sites which served as receiving hospitals and participating blood banks and pharmacies are listed in *Appendix 1*.

Randomisation

Sequence generation

Randomisation was provided by a computer-generated programme at the Birmingham Clinical Trials Unit (BCTU), with a 1 : 1 ratio of experimental intervention and control. The randomisation procedure was stratified by IDS to account for variation in trauma care and type of trauma between sites.

Allocation concealment

Blood banks were supplied with pre-printed 'treatment box number' labels. A registered user at the blood bank requested a treatment allocation from the BCTU and received a treatment box number and treatment arm allocation. The allocated trial intervention was placed into transport boxes affixing the correct labels. These transport boxes were then issued as a pair, one marked red (containing either 2 units of RBC or 2 bags of 250 ml 0.9% saline) and one marked yellow (containing either 2 units of LP or 2 bags of 250 ml 0.9% saline). These sealed boxes were then dispatched to the PHEM base where they were taken to the scene of any pre-hospital trauma patient(s). The weight and appearance of the boxes were the same between trial arms. Those assessing eligibility were blinded to the trial intervention before enrolling patients into the trial. No formal assessment of the success of allocation concealment was undertaken.

Interventions

The experimental intervention was a combination of universal donor (blood group O) RBCs and LyoPlas. LyoPlas was used as the plasma product for this trial (License PEI.H.03075.01.1, Germany) in accordance with MHRA approval for import and use as an investigational medicinal product (IMP). The control intervention was 0.9% saline, which was the most commonly delivered non-blood product fluid at the time of trial design.[3] Participants received up to four boluses of the assigned intervention in order to achieve SBP ≥90mmHg or a palpable radial pulse. For the experimental intervention, this was delivered as alternating units of RBC and LyoPlas until a total of 2 RBC and 2 LyoPlas were delivered. For the control intervention, up to four boluses of 250 ml 0.9% saline were delivered. All boluses were administered using fluid warming devices. If any further fluid resuscitation was required in either interventional arm of the trial, this was given in further boluses of 250 ml 0.9% saline and recorded on the PHEM case report form.

Storage and delivery

Lyophilised plasma should be stored between 2 and 25°C and RBC between 2 and 6°C. As LyoPlas is very difficult to reconstitute when cold, it was necessary to store it separately from the RBC. The trial tested and validated two insulated box systems for this purpose – ORCA boxes (Intelsius, Elvington, UK) and Credo boxes (Pelican BioThermal, Leighton Buzzard, UK). The latter boxes were preferred by air ambulances due to their smaller size and weight. The insulated boxes were preconditioned for a minimum of 24 hours in a freezer below –25°C, then removed 30 minutes before use to allow them to reach the required operating temperature before packing. Each transport container also had a temperature data logger, the choice of which was determined by the local blood bank. Sealed treatment boxes were transferred from blood banks to air ambulance/ambulances bases by volunteers from the Blood Bikes charity (www.bloodbikes.org.uk, accessed 9 February 2022). The intervention pathway is shown in *Figure 3*.

Outcomes

Primary outcome

The primary outcome was a composite measure consisting of episode mortality and lactate clearance defined as a failure to achieve lactate clearance ≥20% per hour in the first 2 hours from randomisation.

Therefore, if the participant experiences either:

1. Episode mortality, or
2. 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.

Rationale for the primary outcome

RePHILL was designed to assess the superiority of pre-hospital blood and plasma transfusion over the existing standard of care at the time, which was 0.9% saline. We hypothesised that early blood would accelerate the reversal of hypovolaemic shock, improve coagulopathy and thereby improve episode mortality.

The absence of a core outcome set for trauma trials creates a challenge for investigators each time they plan and develop a trial. The trial team carefully considered using mortality as the sole and

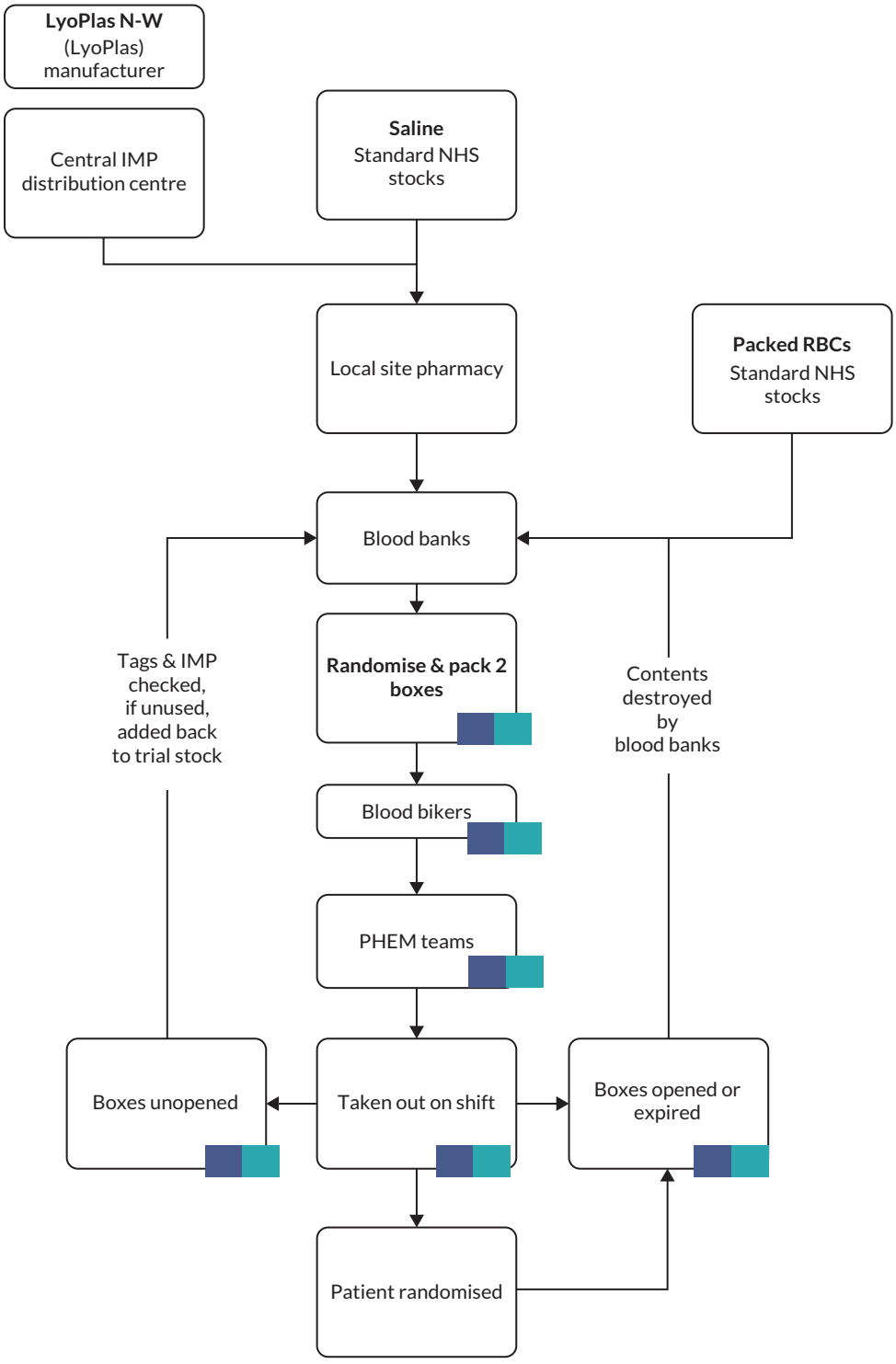

FIGURE 3 IMP management.

primary outcome for the study but were concerned that mortality was too a blunt a tool to assess the effectiveness of the intervention as a certain proportion of patients recruited would either be too well or too sick to benefit from the treatment. Furthermore, sample size estimates to detect small but important differences in mortality were prohibitively large (several thousand participants).

After a review of the literature and further discussion with the funder and co-investigators, it was agreed to use lactate clearance as (1) it could be easily measured; (2) it is related to tissue perfusion, a target specifically related to the intervention; and (3) it has been shown to be prognostically related to mortality.[16]

During the peer review process and contracting with the funder, we were required to include mortality and thus create a composite outcome.

The investigators appreciate that interpretation of a composite outcome is challenging, particularly when the clinical importance of the outcomes is different. We attempt to mitigate this through reporting the individual components of the primary outcome separately in accordance with recommended practice for composite outcomes.

Definitions of components of primary outcome

Episode mortality was defined as those participants who die during the study between the 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.

Lactate clearance was calculated according to the baseline capillary lactate (recorded immediately prior to intervention delivery), and measured using a point of care lactate device. The value, date, and time of the 2-hour post-randomisation lactate concentration were defined as the value, date and time of either:

1. the capillary lactate concentration taken if the participant has not reached hospital within 2 hours of randomisation; or
2. the venous lactate concentration taken in ED if the participant has reached hospital within 2 hours of randomisation; or
3. the 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 (1) to (3) 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:

Lac_0	=	Randomisation capillary lactate concentration
Lac_h	=	2-hour post-randomisation lactate concentration
T_0	=	Date and time of Lac_0
T_h	=	Date and time of Lac_h
Interval	=	T_h–T_0 (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 (T_h)	-	Date and time of the randomisation capillary lactate concentration (T_0)

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

$$LactateClearance(\%per\ hour) = \frac{100x(Lac_0 - Lac_h)}{Lac_0 x \frac{(T_h - T_0)}{60}} \quad (1)$$

A normal lactate is taken to be ≤2.2 mmol/L. Achieving ≥20% per hour lactate clearance is defined as follows in participants whose:

1. Lac_0 is >2.2 mmol/L and whose Lac_h demonstrates lactate clearance of ≥20% per hour; or
2. Lac_h is >2.2 mmol/L, but whose Lac_h is ≤2.2 mmol/L, regardless of the magnitude of the change; or
3. Lac_0 and Lac_h are both ≤2.2 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 *Table 2*.

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

1. Whose Lac_0 is >2.2 mmol/L and whose Lac_h demonstrates lactate clearance of <20% per hour; or
2. Who die prior to interval sampling (e.g. before the Lac_h measurement is taken at T_h). 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 3* below summarises what is considered an event (failure to achieve lactate clearance).

There are instances where the lactate value is too high for a value to be reported, that is 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 was undertaken 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 two- hour randomisation lactate is ≤2.2, then as per the table above the participant would be considered to have achieved clearance; or if both the randomisation and two- 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 was considered missing.

TABLE 2 Lactate clearance

Lac_0 (mmol/L)	Lac_h (mmol/L)	Required lactate clearance
>2.2	>2.2	≥20% per hour
>2.2	≤2.2	Not applicable
≤2.2	≤2.2	Not applicable

TABLE 3 Failure to achieve lactate clearance

Lac_0 (mmol/L)	Lac_h (mmol/L)	Lactate clearance <20% per hour	Lactate clearance ≥20% per hour
>2.2	>2.2	Failure to clear (event)	Achieves clearance
>2.2	≤2.2	Achieves clearance	Achieves clearance
≤2.2	≤2.2	Achieves clearance	Achieves clearance
Dies prior to interval sampling and within 2.5 hours of randomisation		Failure to clear (event)	

Secondary outcomes

The secondary outcomes comprised:

- 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 (SBP, heart rate, capillary oxygen saturation);
- (venous) lactate concentration;
- haemoglobin concentration on ED arrival;
- trauma-induced coagulopathy [defined as International Normalised Ratio (INR) >1.5];
- coagulation measured viscoelastically by rotational thromboelastometry (ROTEM)III;
- platelet function using multiple electrode impedance aggregometry (MultiPlate)III;
- total blood product receipt;
- acute respiratory distress syndrome;
- transfusion-related complications;
- organ failure-free days.

Justification of the secondary outcomes

The secondary outcomes were selected to assess whether PHBP improved blood pressure, heart rate and capillary oxygenation on ED arrival, prolonged on-scene time, reduced pre-hospital fluid and in-hospital transfusion requirements, reduced trauma-induced coagulopathy and preserved platelet function. The study also set out to monitor transfusion-related complications, including acute respiratory distress syndrome and other adverse events.

Definitions of organ failure-free days

The presence of organ failure is defined as any Sequential Organ Failure Assessment (SOFA) component score of ≥3.[3,17] 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.

Sample size calculation

There were no prior published analyses using our composite primary outcome. However, there is considerable evidence from observational data for the survival benefit of RBC and plasma in civilian and military studies. Through consultation with those with expertise in pre-hospital trauma resuscitation, we chose an absolute reduction of 10% in the proportion of patients having one of the components of our composite primary outcome as a clinically meaningful effect size. Therefore, using this difference between proportions (two-sided Fisher's exact test) with 80% power, and a type 1 error rate of 5% (i.e. $\alpha = 0.05$), we calculated a requirement for 219 participants in each arm of the trial (438 participants in total in our 1 : 1 design). A target of 490 patients was set in order to account for 10% loss to follow-up rate.

The interim analysis for the DMC meeting in May 2018 reported the results on the 192 participants recruited by 20 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 did not correspond with the pooled event rate of 15% assumed in the original sample size calculations. On the DMC's recommendations, this issue was discussed with the Trial Steering Committee (TSC) in October 2018. The TSC recommended that the power calculations be 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

(two-sided Fisher's exact test), and a type 1 error rate of 5% (i.e. α = 0.05). This estimated relative risk ratio is consistent with the relative risk ratios of 1.54 and 0.70 reported in two recent pre-hospital RCTs using plasma in one of the treatment arms.[8,9]

Statistical analysis

All analyses followed a statistical analysis plan which was finalised prior to database lock (see *Report Supplementary Material 1*). All analyses were undertaken in SAS v9.4.

Primary analyses

The intention-to-treat principle (i.e. analysis according to the randomisation schedule irrespective of treatment received) informed all primary analyses of the primary and secondary outcomes. Participants who withdrew from the study were non-assessable. A model-based approach to analysis was used with IDS included as a fixed effect covariate in the model. Treatment effects are presented with two-sided 95% confidence intervals (CIs). No adjustment for multiple comparisons was made. The risk ratio and absolute risk difference are adjusted for IDS. In the primary analyses of the primary outcome, all lactate clearance measurements are included regardless of whether they were inside the two hour ± 30 minute window. The 0.9% saline treatment arm is the reference level.

The study reports both the relative effect and absolute effect for binary outcomes (e.g. primary outcome and the individual components) as recommended by CONSORT. Binary outcomes were analysed using log-binomial regression models to obtain adjusted relative risks along with 95% CIs. A relative risk <1 favoured the RBC/LyoPlas group. Adjusted risk differences along with 95% CIs were estimated using a binomial regression model with identity link. A risk difference <0 favoured the RBC/LyoPlas group. Continuous data were analysed using linear regression models to obtain adjusted mean differences between groups along with 95% CIs.

Bayesian analysis

We planned a priori a Bayesian analysis of the primary outcome and its individual components using non-informative, sceptical and informative priors.

Subgroup analysis

We also planned a priori various exploratory subgroup analyses according to: IDS, mode of transport (air vs. ground), initial lactate concentration (≤2.2 mmol/L vs. >2.2 mmol/L), time to hospital arrival 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), presence of head injury, compressible haemorrhage, prior history of anticoagulant/antiplatelet use (anticoagulant or antiplatelet medication vs. no anticoagulant or antiplatelet medication) and cardiac arrest (arrested vs. not arrested).

Sensitivity analyses

Sensitivity analyses were undertaken for the primary outcome:

- An analysis in which the risk ratio and absolute risk difference for the composite outcome were both adjusted for IDS and the following prognostic variables: age, capillary lactate, cardiac arrest and Glasgow Coma Score (GCS) at randomisation.
- A per-protocol analysis, the per-protocol population comprised those who received one or more dose of the randomised intervention/control, unless there was a clinical justification for withholding it.
- An analysis in which only lactate concentrations recorded within specified time windows were included.
- A multiple imputation analysis to assess the effect of missing response.

Post-hoc analyses

Post-hoc analyses comprised a comparison of total transfusion volume (i.e. pre-hospital and hospital transfusion), the influence of injury severity score and transport time from scene to hospital (post-hoc subgroup analyses), and an additional per-protocol analysis in which the per-protocol population was defined as those who received one or more units of the randomised intervention.

We also modelled different scenarios had the trial achieved the intended sample size.

Interim analyses and stopping guidelines

An independent DMEC was established to oversee the safety of trial participants. The DMEC met prior to the trial opening and again once the first 25 patients had been entered into the study. All data discussed remained confidential except to members of the DMEC and the trial statisticians performing the analyses. The DMEC then met on an annual basis throughout the trial. Interim analyses were provided to the DMEC, as well as any new evidence from other sources that may have shown that one treatment was definitely more, or less, effective than the other. The trial would be stopped if the DMEC had advised the TSC that any of the randomised comparisons in the trial had provided both (1) 'proof beyond reasonable doubt' 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 end-points, and (2) 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 trial statistician performed all of the interim and final analyses. Analyses were verified and reviewed by an independent statistician, and the statistical analysis report was reviewed by the senior statistician on the study.

Chapter 3 Results

Internal pilot

There were delays in starting the trial due to changes to the regulatory requirements, change of chief investigator and difficulty in procuring LyoPlas for use in the trial. The trial opened to recruitment at the Midlands Air Ambulance and West Midlands Ambulance sites on 29 November 2016, with the first patient being recruited on 6 December 2016. By 31 May 2017:

- Twenty-six participants had been randomised across the two active sites.
- 100% of patients randomised to the PHBP arm have received at least one unit of RBC and one unit of LyoPlas.
- A review of 22 completed case report forms confirmed 100% data completion for the primary outcome and 93% data for the secondary outcome.
- The TSC and DMC reviewed trial progress and recommended to the funder that the trial be continued.

The funder confirmed successful completion of the internal pilot and approved progression to the main trial.

Recruitment

Following successful completion of the pilot, the trial extended to the three remaining additional sites. Participant recruitment continued through to 1 January 2021. The trial was closed on 2 January 2021 prior to achieving the intended sample size due to the ongoing impact of the COVID-19 pandemic. The decision to close the trial was made by the TSC and sponsor, without any knowledge of the data or results of interim analyses. During the 49 months of trial recruitment, at least 580 patients were assessed for eligibility, with 432 (74%) deemed eligible and recruited into the trial (see *Figure 4*).

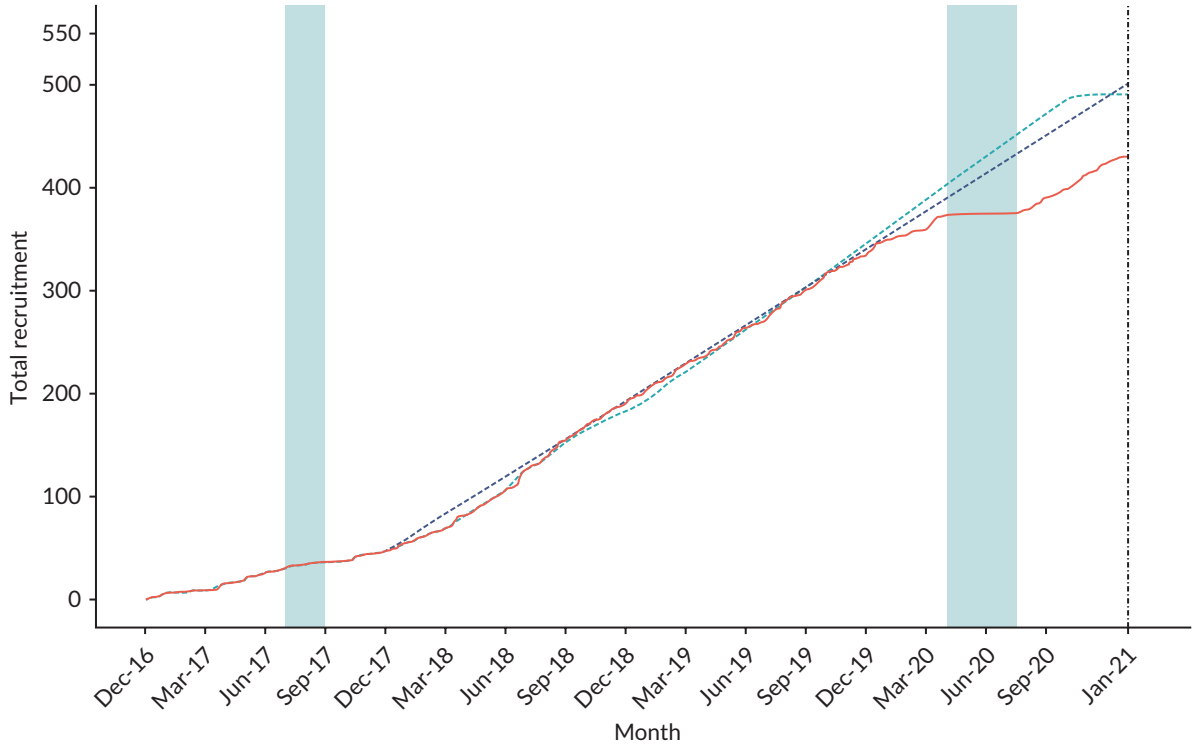

FIGURE 4 Recruitment. Thick red line denotes observed recruitment. Aqua line denotes the revised target recruitment still based on a total of 490. Dashed blue line denotes projected recruitment based on rate observed up to the previous DMEC meeting in January 2020. Lighter aqua shaded region denotes period during which no LyoPlas was available to be supplied to the trial. Dashed black line denotes the scheduled end of trial recruitment. Darker aqua shaded region denotes period during which recruitment was paused due to COVID-19. A further breakdown of recruitment (by site) is provided in *Appendix 2*.

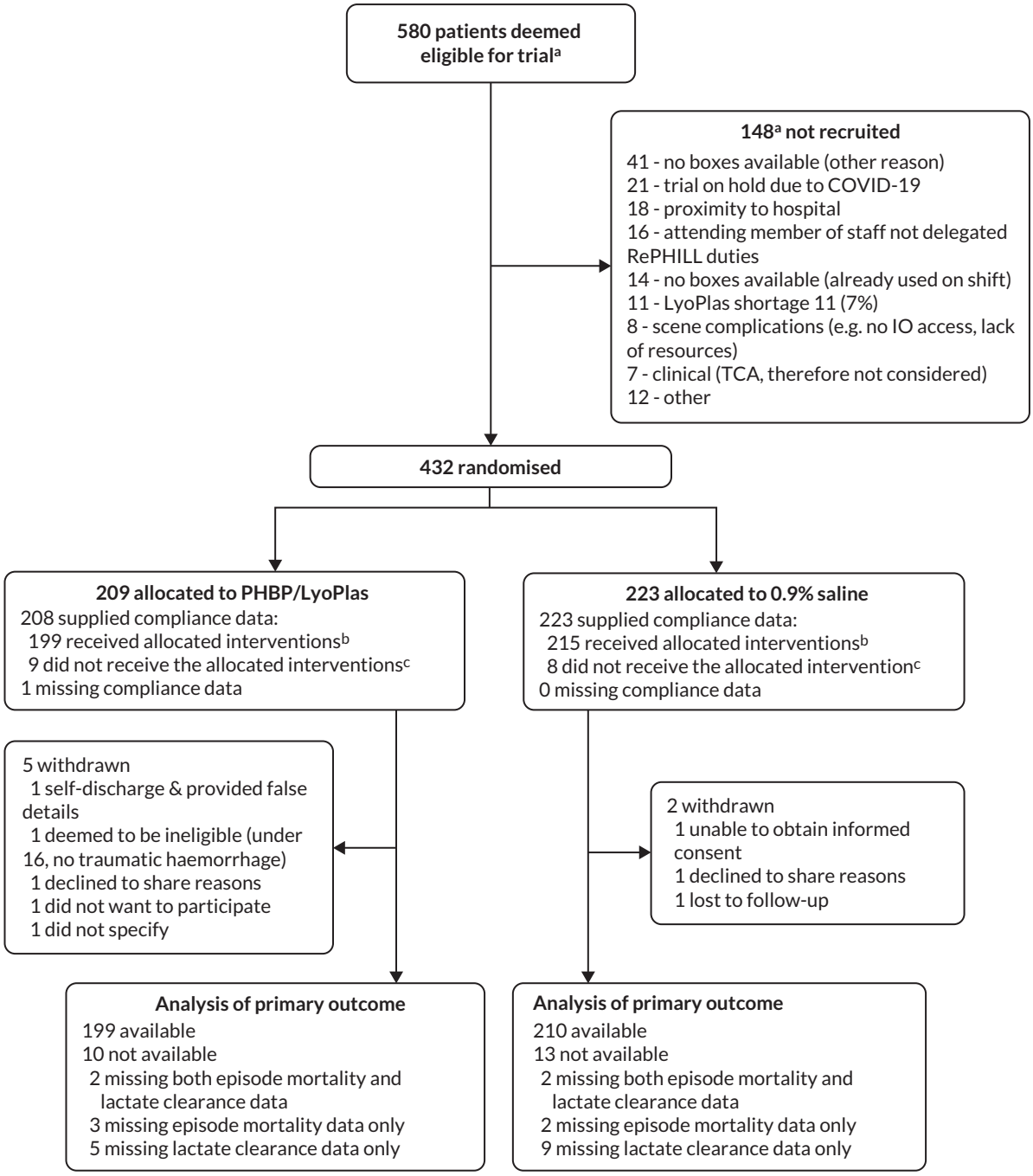

FIGURE 5 CONSORT flow diagram. [a]based on screening lists provided by each IDS. IO = intraosseous, TCA = traumatic cardiac arrest. [b]allocated interventions are, unless clinically justified: the administration of at least one unit of RBC and one unit of LyoPlas in the PHBP/LyoPlas arm of the trial, and the administration of at least one bolus of fluid in the 0.9% saline arm of the trial. [c]reasons for participants not receiving any units of allocated intervention (with no clinical justification) were: 9 due to equipment absence/failure (e.g. of giving sets or lactate monitors), 1 due to complex scene conditions, 1 due to decision to stop resuscitation, 1 due to non-trial saline already being administered to patient and 5 gave no reason.

The flow of participants and reasons for non-recruitment are summarised in *Figure 5*. Recruitment was approximately equal between both trial arms with 209 (46%) participants allocated to receive RBC/LyoPlas and 223 (54%) allocated to receive 0.9% saline.

All participants were followed up until trial exit, with data collection ending at the first occurrence of: withdrawal, acute care discharge, death or at 30 days follow-up. Episode mortality data was collected

up to discharge from the acute care setting, which may be >30 days. The median duration of study follow-up was 8 days [interquartile range (IQR) to 34] across all 432 participants. The median follow-ups for each treatment group were 9 days (IQR 1 to 34) for participants in the RBC/LyoPlas group and 7 days (IQR 0 to 31) for participants in the 0.9% saline group.

The allocation of participants between treatment arms exhibited a slight imbalance, with 14 more participants allocated to receive 0.9% saline than to receive RBC/LyoPlas. Across all 8188 treatment boxes issued by the blood banks, 4094 contained 0.9% saline and 4094 contained RBC/LyoPlas. Treatment boxes issued by blood banks were split 50:50 between RBC/LyoPlas and 0.9% saline in each IDS. Although the proportion of issued treatment boxes used by participants did vary by IDS, from 2.8% to 11.5%, there was no systematic imbalance by study arm. The pre-hospital teams were unaware of the treatment allocation prior to enrolling a participant, so we assume that the imbalance in the number of participants in each arm is down to random chance.

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics by treatment arm are presented in *Table 4*. Participants were well-balanced across baseline characteristics, with most participants being male (82%), of white ethnicity (62%) and with a median age of 38 years (IQR 26 to 58). Participants could record more than one injury mechanism and the most commonly recorded was road traffic collision (62%), with stabbing (16%) and falls (14%) being the other main mechanisms of injury. Other mechanisms of injury were recorded by 9% of participants and comprised 13 laceration injuries, 6 pedestrian incidents with trains, 4 agricultural incidents, 4 industrial accidents and 5 other injuries.

Injury characteristics were similar across treatment arms. The presence of a concurrent brain injury was only collected in the last 16 months of the trial and, during that period, around half of the participants had a concurrent brain injury (48%). Participants could experience both compressible and non-compressible haemorrhages, with non-compressible haemorrhages being the most commonly recorded (83%). Traumatic cardiac arrest, defined as those with a heart rate of 0 and blood pressure of 0, was experienced by 13% of participants providing on-scene heart rate and blood pressure measurements. Blunt force trauma injuries were recorded in 79% of participants, with penetrating trauma injuries recorded in 22% of participants. Acute excessive consumption or alcoholism was suspected in 14% of participants, and the presence of other illicit substances was suspected in 6% of participants. On-scene vital signs were very similar between both groups, with participants exhibiting a mean [(standard deviation (SD)] blood pressure of 73 (18)/46 (15) mmHg, a mean (SD) heart rate of 112 (32) bpm, a mean (SD) respiratory rate of 23.8 (10.1) per minute, a mean (SD) oxygen saturation of 92% (9%) and a median (IQR) GCS of 7 (3, 14). Capillary lactate concentration was very similar across both groups, with a mean (SD) of 9.15 (4.69) mmol/L across all participants.

Both measures of injury severity, injury severity score (ISS) and new injury severity score (NISS), are recorded only on those participants that were Trauma Audit Research Network (TARN) eligible. This excludes participants who died prior to arrival at the ED, so cannot strictly be defined as a baseline characteristic. For the 300 participants providing injury severity scores, the median ISS was 36 (IQR 25 to 50) and median NISS was 43 (IQR 34 to 57). The pre-hospital teams enrolling RePHILL patients attended scene via road ambulance for 62% of participants. They arrived on scene at a median of 26 minutes (IQR 19 to 37) after the time of injury, approximated via the time of the 999 call, and administered the first bolus of trial intervention at a median of 22 minutes (IQR 15 to 34) later.

TABLE 4 Baseline characteristics by group

	RBC/LyoPlas (*n* = 209)	0.9% saline (*n* = 223)	All (*n* = 432)
Stratification variable			
IDS			
Site 1	68 (32%)	64 (29%)	132 (31%)
Site 2	37 (18%)	41 (18%)	78 (18%)
Site 3	60 (29%)	61 (27%)	121 (28%)
Site 4	44 (21%)	57 (26%)	101 (23%)
Demographic and other baseline variables			
Sex	**(*n* = 208)**	**(*n* = 223)**	**(*n* = 431)**
Male	170 (82%)	183 (82%)	353 (82%)
Age (n)	**(*n* = 196)**	**(*n* = 211)**	**(*n* = 407)**
Median (IQR)	38 (27, 56.5)	39 (24, 59)	38 (26, 58)
Ethnic group[a]	**(*n* = 166)**	**(*n* = 168)**	**(*n* = 334)**
White	104 (63%)	104 (62%)	208 (62%)
Black	2 (1%)	3 (2%)	5 (1.5%)
Mixed	4 (2%)	5 (3%)	9 (3%)
Asian	8 (5%)	8 (5%)	16 (5%)
Other	1 (1%)	4 (2%)	5 (1.5%)
Not known/provided	47 (28%)	44 (26%)	91 (27%)
Injury details			
Injury mechanism[b]			
RTC	130 (62%)	139 (62%)	269 (62%)
Stabbing	33 (16%)	35 (16%)	68 (16%)
Fall	26 (12%)	35 (16%)	61 (14%)
Gunshot	4 (2%)	4 (2%)	8 (2%)
Burn	0 (0%)	1 (0.4%)	1 (0.2%)
Inhalation	1 (0.5%)	0 (0%)	1 (0.2%)
Other[c]	19 (9%)	22 (10%)	41 (9%)
Injury characteristics			
Concomitant head injury[d]	29/60 (48%)	32/68 (47%)	61/128 (48%)
Compressible haemorrhage	50/208 (24%)	49/223 (22%)	99/431 (23%)
Non-compressible haemorrhage	171/208 (82%)	186/223 (83%)	357/431 (83%)
Traumatic cardiac arrest[e]	21/151 (14%)	20/175 (11%)	41/326 (13%)
Blunt force trauma	162/208 (78%)	178/223 (80%)	340/431 (79%)
Penetrating trauma	47/208 (23%)	48/223 (22%)	95/431 (22%)
Crush trauma	6/208 (3%)	2/223 (1%)	8/431 (2%)

TABLE 4 Baseline characteristics by group (*continued*)

	RBC/LyoPlas (*n* = 209)	0.9% saline (*n* = 223)	All (*n* = 432)
Suspected at time of injury			
Alcohol			
Yes	30 (14%)	32 (14%)	62 (14%)
No	175 (84%)	186 (83%)	361 (84%)
Other illicit substances			
Yes	13 (6%)	12 (5%)	25 (6%)
No	187 (89%)	201 (90%)	388 (90%)
Pre-hospital timeline			
Time from 999 call to arrival on scene (mins) Median (IQR) (n)	26 (19–36) (209)	27 (19–37) (223)	26 (19–37) (432)
Time from arrival on scene to administration of first intervention (mins) Median (IQR) (n)	22 (15–33) (201)	21 (13–35) (209)	22 (15–34) (410)
On-scene vital signs			
Heart Rate (bpm)[f] Mean (SD, n)	115 (31, 185)	109 (33, 198)	112 (32, 383)
SBP (mmHg)[f] Mean (SD, n)	73 (16, 128)	73 (20, 148)	73 (18, 276)
DBP (mmHg)[f] Mean (SD, n)	47 (13, 125)	46 (16, 147)	46 (15, 272)
Respiratory rate (/min)[f] Mean (SD, n)	24 (9, 172)	23 (11, 186)	24 (10, 358)
Oxygen saturation (%)[f] Mean (SD, n)	92 (8, 131)	91 (9, 144)	92 (9, 275)
GCS Median (IQR) (n)	8 (3–14) (209)	6 (3–14) (222)	7 (3–14) (431)
Capillary lactate concentration (mmol/L) Mean (SD, n)	9.1 (4.4, 199)	9.2 (5.0, 207)	9.2 (4.7, 406)
Medical history[g]			
ISS[h] Median (IQR) (n)	36 (24.5–49) (148)	36 (25–50) (152)	36 (25–50) (300)
NISS[h] Median (IQR) (n)	43 (34–57) (144)	48 (34–57) (148)	43 (34–57) (292)
Comorbidities			
Yes	18/172 (10%)	20/170 (12%)	38/342 (11%)
No	154/172 (90%)	149/170 (87.5%)	303/342 (88.75%)
Anticoagulant medication			
Yes	16/172 (9%)	24/170 (14%)	40/342 (12%)
No	125/172 (73%)	105/170 (62%)	230/342 (67%)
Unknown	30/172 (17.5%)	41/170 (24%)	71/342 (20.75%)
Antiplatelet medication			
Yes	3/172 (2%)	3/170 (2%)	6/342 (1.75%)
No	138/172 (80%)	127/170 (75%)	265/342 (78%)
Unknown	30/172 (17.5%)	40/170 (23%)	70/342 (20%)
Concomitant treatments			
Tranexamic acid	182 (87%)	206 (92%)	388 (90%)

continued

TABLE 4 Baseline characteristics by group (*continued*)

	RBC/LyoPlas (*n* = 209)	0.9% saline (*n* = 223)	All (*n* = 432)
Fluid volume given prior to intervention (ml) Mean (SD)	422 (499)	437 (482)	430 (490)
Mode of transport			
Air	80 (38%)	86 (39%)	166 (38%)
Ground	129 (62%)	137 (61%)	266 (62%)

a Data only available for participants providing an ED arrival form.
b Multiple responses are possible.
c Other injuries comprise: 13 laceration injuries, 6 pedestrian incidents with trains, 4 agricultural incidents, 4 industrial accidents and 5 other injuries.
d Added in v4.0 of pre-hospital CRF (sent to all sites by 29 August 2019).
e Defined as those with a heart rate of 0 and blood pressure of 0.
f Blood pressure, heart rate, respiratory rate and oxygen saturation are summarised as continuous variables only for participants with non-zero on-scene measurements.
g Data only available for the 342 participants providing a medical history form.
h ISS and NISS will only be available for those participants who are TARN eligible, hence this is not strictly a baseline characteristic, and the number of missing participants refers to the number of TARN eligible participants missing their ISS or NISS.

Mode of transport

There was variability between IDS in the mode of transport the pre-hospital teams enrolling RePHILL patients used to attend the scene (see *Table 3*). Over all participants, 62% were attended via road ambulance, but this proportion varies between 48% and 71% across the four IDS.

The distribution of mode of transport is summarised by IDS and treatment group in *Table 5*.

Pre-hospital timeline

The pre-hospital timeline (see *Table 6*) displays the time, in minutes, between the key trial events that occurred prior to arrival at hospital for each treatment group. The timings are very similar across the two treatment groups, with little evidence that administering boluses of RBC and LyoPlas, compared to 0.9% saline, delayed arrival at ED. The time from opening the treatment box to arrival at ED was a median of 32 minutes (IQR 21 to 45) for participants in the RBC/LyoPlas group and a median of 30 minutes (IQR 20 to 45) for participants in the 0.9% saline group.

TABLE 5 Mode of transport by IDS and group

Site	Mode of transport	RBC/LyoPlas (%)	0.9% saline (%)	Total (%)
Site 1	Air	19/68 (28)	19/64 (30)	38/132 (29)
	Ground	49/68 (72)	45/64 (70)	94/132 (71)
Site 2	Air	17/37 (46)	18/41 (44)	35/78 (45)
	Ground	20/37 (54)	23/41 (56)	43/78 (55)
Site 3	Air	23/60 (38)	17/61 (28)	40/121 (33)
	Ground	37/60 (62)	44/61 (72)	81/121 (67)
Site 4	Air	21/44 (48)	32/57 (56)	53/101 (52)
	Ground	23/44 (52)	25/57 (44)	48/101 (48)

TABLE 6 Pre-hospital timing by group. Values above the diagonal correspond to participants allocated to RBC/LyoPlas, values below the diagonal correspond to participants allocated to 0.9% saline

Pre-hospital event	999 call	On-scene attendance	Randomisation capillary lactate	Treatment box opening	Left scene[a]	Arrival at ED[b]
999 call		26 (19, 36) (*n* = 209)	46 (35, 60) (*n* = 203)	47 (35, 62) (*n* = 209)	57.5 (41, 76) (*n* = 62)	83 (63, 109) (*n* = 169)
On-scene attendance	27 (19, 37) (*n* = 223)		18 (11, 28) (*n* = 203)	19 (11, 30) (*n* = 209)	31 (22, 45) (*n* = 62)	57 (40, 78) (*n* = 169)
Randomisation capillary lactate	48.5 (34, 65) (*n* = 214)	17.5 (10, 30) (*n* = 214)		0 (0, 1) (*n* = 203)	4 (0, 19) (*n* = 59)	33 (22, 47) (*n* = 165)
Treatment box opening	48 (34, 65) (*n* = 223)	19 (10, 31) (*n* = 223)	1 (0, 2) (*n* = 214)		3 (−2, 15) (*n* = 62)	32 (21, 45) (*n* = 169)
Left scene[a]	66 (42, 87.5) (*n* = 68)	34.5 (19, 45) (*n* = 68)	10 (−3, 24.5) (*n* = 64)	10.5 (−3, 24.5) (*n* = 68)		26 (17, 36) (*n* = 53)
Arrival at ED[b]	85 (66, 111) (*n* = 171)	57 (41, 74) (*n* = 171)	31 (21, 45) (*n* = 167)	30 (20, 45) (*n* = 171)	26.5 (18, 36.5) (*n* = 56)	

All durations are recorded in minutes and expressed as medians and IQRs.
a Added in v4.0 of pre-hospital CRF (active from 29th August 2019).
b These numbers are lower than the totals of randomised participants due to deaths on-scene or during transit to hospital.

Primary outcomes

The composite primary outcome of episode mortality and/or failure to clear lactate occurred in 128/199 (64%) of participants in the RBC/LyoPlas group, and in 136/210 (65%) of participants in the saline 0.9% group (see *Table 5*). After adjusting for IDS, allocation to treatment with RBC/LyoPlas was observed across the 432 study participants to have a 1% higher relative risk of episode mortality and/or failure to clear lactate than allocation to treatment with 0.9% saline with a 95% two-sided compatibility interval of 0.88 to 1.17, indicating a moderate range of plausible true treatment effects. The degree of evidence against the null hypothesis that the treatments are interchangeable is $p = 0.86$. After adjusting for IDS, allocation to treatment with RBC/LyoPlas was observed across the 432 study participants to have a 0.025% lower absolute risk of episode mortality and/or failure to clear lactate than allocation to treatment with 0.9% saline with a 95% two-sided compatibility interval of −9% to 9%, indicating a moderate range of plausible true treatment effects. The degree of evidence against the null hypothesis that the treatments are interchangeable is $p = 0.996$.

The qualifying events for the primary outcome in each treatment group are given in *Table 7*. Due to participant drop-out and missing data, 23 participants did not provide primary outcome data. For the 199 participants providing a primary outcome in the RBC/LyoPlas group, the most common outcome was survival and clearance of lactate (36%), 29% of participants experienced episode mortality and failed to clear their lactate, 20% survived but failed to clear their lactate and 15% cleared their lactate but experienced episode mortality. For the 210 participants providing a primary outcome in the 0.9% saline group, the most common outcome was experiencing episode mortality and failure to clear their lactate (36%), 35% of participants survived and cleared their lactate, 18% survived but failed to clear their lactate and 11% cleared their lactate but experienced episode mortality.

TABLE 7 Summary of qualifying event that contributed to the primary outcome

	RBC/LyoPlas (%)	0.9% saline	Total
Qualifying event, n (%)			
Both episode mortality and failure to clear lactate	58/209 (28)	76/223 (34)	134/432 (31)
Episode mortality alone	30/209 (14)	23/223 (10)	53/432 (12)
Failure to clear lactate alone	40/209 (19)	37/223 (17)	77/432 (18)
Alive and cleared lactate	71/209 (34)	74/223 (33)	145/432 (34)
Missing/not available	10/209 (5)	13/223 (6)	23/432 (5)

TABLE 8 Primary outcomes

	RBC/LyoPlas (%)	0.9% saline (%)	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Primary outcome				
Episode mortality and/or failure to clear lactate	128/199 (64)	136/210 (65)	1.01 (0.88 to 1.17)[a]; *P* = 0.86	−0.025% (−9% to 9%)[b]; *P* = 0.996
Episode mortality	88/203 (43)	99/218 (45)	0.97 (0.78 to 1.20)[a]; *P* = 0.75	−3% (−12% to 7%)[b]; *P* = 0.57
Failure to clear lactate	98/196 (50)	113/206 (55)	0.94 (0.78 to 1.13)[a]; *P* = 0.52	−5% (−14% to 5%)[b]; *P* = 0.33

Data are n/N (%);
a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate lower event rates in the RBC/LyoPlas group.
b Output is from a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 lower event rates in the RBC/LyoPlas group.

The individual components of the primary outcome were analysed separately (see *Table 8*). Episode mortality occurred in 88/203 (43%) of participants in the RBC/LyoPlas group, and in 99/218 (45%) of participants in the saline 0.9% group (see *Table 8*). Analyses, adjusted for IDS, yielded an estimated risk ratio of 0.97 (95% CI 0.78 to 1.20; *p*-value: 0.75) and an estimated risk difference of −3% (95% CI: −12% to 7%; *p*-value: 0.57). Failure to clear lactate occurred in 98/196 (50%) of participants in the RBC/LyoPlas group, and in 113/206 (55%) of participants in the saline 0.9% group (see *Table 8*). Analyses, adjusted for IDS, yielded an estimated risk ratio of 0.94 (95% CI 0.78 to 1.13; *p*-value: 0.52) and an estimated risk difference of −5% (95% CI −14% to 5%; *p*-value: 0.33). The estimates of treatment effects for each individual component produced relatively wide CIs including both benefits and harms. The degree of evidence against the null hypothesis that the treatments are interchangeable ranged from 0.33 to 0.75 across these analyses.

Table 6 summarises which of the primary outcome components were met by the 432 participants: the 409 who recorded a primary outcome, and the 23 who did not provide information to determine a primary outcome.

Secondary outcomes

The secondary outcomes are summarised in *Tables 9–13*. Selected secondary outcomes are summarised in *Table 9*. The volume of post intervention fluids was similar between treatment groups [adjusted mean

TABLE 9 Selected secondary outcomes

	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Secondary outcomes				
Post intervention fluids (ml)	123 (310), 207	160 (389), 221		−34 (−101 to 32)[a]; *P* = 0.31
Time to ED arrival (mins)				
From 999 call	90 (35), 169	91 (35), 171	-	0.60 (−6.14 to 7.35)[a]; *P* = 0.86
From randomisation	37 (22), 169	35 (22), 171	-	3.03 (−1.40 to 7.46)[a]; *P* = 0.18
Vital signs at ED arrival				
Heart rate (bpm)	107 (29), 157	105 (24), 154	-	−0.80 (−5.83 to 4.23)[b]; *P* = 0.76
SBP (mmHg)	114 (27), 111	114 (29), 124	-	−1.19 (−8.19 to 5.82)[b]; *P* = 0.74
Diastolic blood pressure (mmHg)	75 (24), 107	72 (24), 123	-	2.26 (−3.77 to 8.29)[b]; *P* = 0.46
Respiratory rate (/min)	20 (6.5), 128	19 (5.6), 126	-	0.59 (−0.79 to 1.97)[b]; *P* = 0.40
Oxygen saturation (%)	97 (5.2), 105	97 (5.2), 114	-	0.48 (−0.86 to 1.82)[b]; *P* = 0.48
Laboratory results (ED arrival)				
Lactate concentration (mmol/L)	7.04 (4.50)	6.93 (4.58)	-	−0.08 (−0.97 to 0.82)[b]; *P* = 0.87
INR >1.5	12/84 (14%)	12/74 (16%)	0.91 (0.44 to 1.90)[c]; *P* = 0.80	
Haemoglobin (g/L)	133 (19), 154	118 (23), 152	-	15 (10 to 19)[a]; *P* < 0.0001
Total blood product up to 24 hours after ED arrival				
RBC	6.34 (7.09), 209	4.41 (6.17), 223	-	1.80 (0.58 to 3.01)[a]; *P* = 0.0037
Plasma	5.04 (5.56), 209	3.37 (5.04), 223	-	1.54 (0.57 to 2.50)[a]; *P* = 0.0018
Death				
Within 3 hours	32/197 (16%)	46/208 (22%)	0.75 (0.50 to 1.13)[c]; *P* = 0.17	−7% (−15% to 1%)[d]; *P* = 0.083
Within 30 days	86/204 (42%)	99/219 (45%)	0.94 (0.76 to 1.17)[c]; *P* = 0.59	−4% (−13% to 6%)[d]; *P* = 0.44
Within 24 hours	47/197 (24%)	65/207 (31%)	0.77 (0.56 to 1.06)[c]; *P* = 0.10	−8% (−17% to 0.05%)[d]; *P* = 0.066

Data are n/N (%); or mean (SD), N, when N is different to the total number of participants, unless otherwise specified.

a Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group

b Output is from a linear regression model adjusted for IDS and the on-scene value of the outcome variable. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.

c Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate lower event rates in the RBC/LyoPlas group.

d Output is from a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 lower event rates in the RBC/LyoPlas group.

difference −34 ml (95% CI −101 to 32)]. There was little evidence of any meaningful difference in the time taken to arrive at ED from either the time of injury [recorded as the time of the 999 call, adjusted mean difference 0.60 minutes (95% CI −6.14 to 7.35)] or from the time of randomisation [recorded as the time the first treatment box was opened, adjusted mean difference 3.03 minutes (95% CI −1.40 to 7.46)]. Vital signs recorded at ED arrival were similar across treatment groups [adjusted mean differences for heart rate −0.80 (95% CI −5.83 to 4.23) beats per minute, SBP −1.19 (95% CI −8.19 to 5.82) mmHg, diastolic blood pressure 2.26 (95% CI −3.77 to 8.29) mmHg, respiratory rate 0.59 (95% CI −0.79 to 1.97) per minute and oxygen saturation 0.48 (95% CI −0.86 to 1.82)]. Laboratory results showed that lactate concentration on ED arrival was similar across groups [adjusted mean difference −0.08 (95% CI −0.97 to 0.82) mmol/L]. Although INR was only collected on 158 participants, the proportion with an INR >1.5 was similar across treatment groups [adjusted risk ratio 0.91 (95% CI 0.44 to 1.90)]. Haemoglobin concentration on ED arrival was significantly higher in the RBC/LyoPlas group compared to the 0.9% saline group [adjusted mean difference 15 (95% CI 10 to 19) g/L]. A post-hoc analysis found that blood product use from admission to hospital through to 24 hours later was higher in the RBC/LyoPlas group than in the 0.9% saline group [adjusted mean difference of 1.80 (95% CI 0.58 to 3.01) units of RBCs and 1.54 (95% CI 0.57 to 2.50) units of plasma]. Measures of mortality within 3 hours of injury and within 30 days of mortality were both slightly lower in the RBC/LyoPlas group. Analyses, adjusted for IDS, yielded an estimated risk ratio of 0.75 (95% CI 0.50 to 1.13) and an estimated risk difference of −7% (95% CI −15% to 1%) for 3-hour mortality. For 30-day mortality, adjusted analyses produced an estimated risk ratio of 0.94 (95% CI 0.76 to 1.17) and an estimated risk difference of −4% (95% CI −13% to 6%).

Pre-hospital fluid (type and volume) and vital signs are summarised in *Table 10*. The proportion of participants receiving fluids given prior to intervention, and the volumes of fluids received, were similar between both groups [adjusted risk ratio 0.95 (95% CI 0.83 to 1.07) and adjusted mean difference

TABLE 10 Further secondary and exploratory outcomes: pre-hospital fluid type and volume and vital signs

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Pre-hospital fluid type and volume				
Fluids given prior to intervention	142/209 68%)	159/223 (71%)	0.95 (0.83 to 1.07)[a]; *P* = 0.40	
Saline[b]	140/209 (67%)	159/223 (71%)		
Hartmann's[b]	1/209 (0.5%)	2/223 (1%)		
Other[b]	7/209 (3%)	4/223 (2%)		
Volume given prior to intervention	422 (499), 209	437 (482), 223		−17 (−108 to 74)[c]; 0.71
Fluids given after intervention	40/207 (19%)	52/221 (24%)	0.84 (0.58 to 1.21)[a]; *P* = 0.35	
Saline[b]	33/207 (16%)	39/221 (17%)		
Hartmann's[b]	3/207 (1%)	6/221 (3%)		
Other[b]	5/207 (2%)	15/221 (7%)		
Volume given after intervention	123 (310), 207	160 (389), 221		−34 (−101 to 32)[c]; *P* = 0.31

TABLE 10 Further secondary and exploratory outcomes: pre-hospital fluid type and volume and vital signs (*continued*)

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Vital signs				
Heart rate (bpm)				
On scene	115 (31),185	109 (33), 198		5.83 (−0.61 to 12.27)[c]; *P* = 0.076
ED arrival	107 (29), 157	105 (24), 154		−0.80 (−5.83 to 4.23)[d]; *P* = 0.76
2 hrs after ED arrival	95 (22), 147	91 (22), 147		3.80 (−1.09 to 8.70)[d]; *P* = 0.13
6 hrs after ED arrival	88 (21), 148	86 (21), 137		2.57 (−2.34 to 7.49)[d]; *P* = 0.31
12 hrs after ED arrival	90 (21), 149	89 (23), 139		1.23 (−3.81 to 6.28)[d]; *P* = 0.63
24 hrs after ED arrival	90 (20), 144	90 (22), 134		−1.05 (−5.94 to 3.84)[d]; *P* = 0.67
SBP (mmHg)				
On scene	73 (16), 128	73 (20), 148		−0.05 (v4.23 to 4.14)[c]; *P* = 0.98
ED arrival	114 (27), 111	114 (29), 124		−1.19 (−8.19 to 5.82)[d]; *P* = 0.74
2 hrs after ED arrival	114 (24), 113	115 (21), 121		0.04 (−5.75 to 5.83)[d]; *P* = 0.99
6 hrs after ED arrival	109 (21), 116	114 (23), 117		−5.22 (−10.87 to 0.43)[d]; *P* = 0.070
12 hrs after ED arrival	113 (22), 110	115 (24), 118		−2.27 (−8.23 to 3.69)[d]; *P* = 0.45
24 hrs after ED arrival	114 (20), 109	117 (21), 114		−3.24 (−8.59 to 2.12)[d]; *P* = 0.24
Diastolic blood pressure (mmHg)				
On scene	47 (13), 125	46 (16), 147		0.77 (−2.70 to 4.24)[c]; *P* = 0.66
ED arrival	75 (24), 107	72 (24), 123		2.26 (−3.77 to 8.29)[d]; *P* = 0.46
2 hrs after ED arrival	67 (17), 111	65 (15), 119		2.07 (−1.97 to 6.12)[d]; *P* = 0.31
6 hrs after ED arrival	64 (15), 114	67 (15), 117		−2.76 (−6.57 to 1.04)[d]; *P* = 0.15
12 hrs after ED arrival	62 (13), 108	62 (13), 118		−0.36 (−3.60 to 2.88)[d]; *P* = 0.83
24 hrs after ED arrival	61 (14), 107	62 (12), 114		−1.44 (−4.73 to 1.84)[d]; *P* = 0.36
Respiratory rate (/min)				
On scene	24 (9.5), 172	23 (10.6), 191		0.98 (−1.10 to 3.05)[c]; *P* = 0.36
ED arrival	20 (6.5), 128	19 (5.6), 126		0.59 (−0.79 to 1.97)[d]; *P* = 0.40
2 hrs after ED arrival	19 (4.8), 121	19 (4.7), 123		0.45 (−0.72 to 1.62)[d]; *P* = 0.45
6 hrs after ED arrival	19 (6.3), 133	18 (4.1), 129		0.62 (−0.66 to 1.91)[d]; *P* = 0.34
12 hrs after ED arrival	19 (5.2), 140	18 (3.8), 133		0.49 (−0.59 to 1.58)[d]; *P* = 0.37

continued

TABLE 10 Further secondary and exploratory outcomes: pre-hospital fluid type and volume and vital signs (*continued*)

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
24 hrs after ED arrival	18 (4.11), 140	18 (3.7), 129		0.38 (−0.56 to 1.31)[d]; *P* = 0.43
Oxygen saturation (%)				
On scene	92 (7.6),131	91 (9.3), 144		0.92 (−1.10 to 2.94)[c]; *P* = 0.37
ED arrival	97 (5.2), 105	97 (5.2), 114		0.48 (−0.86 to 1.82)[d]; *P* = 0.48
2 hrs after ED arrival	98 (3.9), 104	98 (4.9), 108		0.03 (−1.14 to 1.20)[d]; *P* = 0.96
6 hrs after ED arrival	98 (4.4), 109	98 (6.0), 103		0.48 (−0.94 to 1.90)[d]; *P* = 0.51
12 hrs after ED arrival	97 (6.9), 108	98 (3.9), 102		−0.38 (−1.91 to 1.15)[d]; *P* = 0.63
24 hrs after ED arrival	97 (2.6), 105	98 (2.4), 96		−0.02 (−0.70 to 0.65)[d]; *P* = 0.95

a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate lower event rates in the RBC/LyoPlas group.
b Multiple responses are possible.
c Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.
d Output is from a linear regression model adjusted for IDS and the on-scene value of the outcome variable. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.

Note
Data are n/N (%); or mean (SD), N, when N is different to the total number of participants, unless otherwise specified.

−17 (−108 to 74) ml]. The proportion of participants receiving fluids given after intervention, and the volumes of fluids received, were also similar between both groups [adjusted risk ratio 0.84 (95% CI 0.58 to 1.21) and adjusted mean difference −34 (−101 to 32) ml]. Vital signs were recorded at regular intervals from arrival on scene to 24 hours after arrival at hospital. Vital signs are only summarised for participants who were still alive at the time of assessments (i.e. no values of 0 are imputed for participants known to have died at a previous time point). All vital signs were broadly similar across both treatment groups at each time point. Mean heart rate values appeared to stabilise at around 86–90 beats per minute two hours after participants arrived in hospital. SBP increased from a mean of 73 mmHg on scene to around 110–117 mmHg at all in-hospital assessments. Diastolic blood pressure increased from a mean of 46 mmHg on scene to a mean of 73 mmHg when arriving at hospital, before reducing to a mean of 62 mmHg 12 hours after arriving at hospital. Respiratory rate was slightly elevated on scene with a mean of 23 per minute, but this reduced to an average rate between 18 and 20 per minute after arrival at hospital. Oxygen saturation was relatively low on scene with a mean of 92%, but this increased to a mean saturation greater than 97% once participants arrived in hospital. Lactate concentration was similar across both arms at each time point with values decreasing from arrival at hospital to 2 hours after arrival at hospital. At 2 and 6 hours after arrival at hospital, the proportion of participants with an INR >1.5 was similar across treatment groups, however given the low incidence of participants with an INR >1.5 there is considerable uncertainty associated with these estimates. Calcium concentration on ED arrival was similar across treatment groups [adjusted mean difference −0.03 (95% CI −0.12 to 0.05) mmol/L].

Total blood product receipt was recorded at 6, 12 and 24 hours after arrival at hospital and is summarised in *Table 12*. The mean number of units of RBCs used at each time point was slightly higher in participants in the RBC/LyoPlas group compared to the 0.9% saline group. Similarly, the mean number of units of plasma used at each time point was also slightly higher in the RBC/LyoPlas group compared to the 0.9% saline group. Participants on the RBC/LyoPlas arm received a higher volume of crystalloid than participants on the 0.9% saline arm [adjusted mean difference at 12 hours after hospital arrival 628

TABLE 11 Further secondary and exploratory outcomes: laboratory results, ROTEM and Multiplate

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Laboratory results				
Lactate concentration (mmol/L)				
2 hrs post-randomisation based on time	5.42 (4.45) (*n* = 168)	5.78 (4.68) (*n* = 169)		−0.37 (−1.28 to 0.53)[a]; *P* = 0.42
2 hrs post-randomisation based on CRF	4.91 (4.14) (*n* = 153)	5.40 (4.41) (*n* = 152)		−0.34 (−1.24 to 0.55)[a]; *P* = 0.46
Arrival at ED	7.04 (4.50) (*n* = 157)	6.93 (4.58) (*n* = 161)		−0.08 (−0.97 to 0.82)[a]; *P* = 0.87
2 hrs after ED arrival	4.45 (3.57) (*n* = 134)	4.46 (3.33) (*n* = 138)		−0.07 (−0.84 to 0.70)[a]; *P* = 0.86
INR >1.5				
ED arrival	12/84 (14%)	12/74 (16%)	0.91 (0.44 to 1.90)[b]; *P* = 0.80	
2 hrs after ED arrival	1/27 (4%)	4/29 (14%)	0.27 (0.03 to 2.25)[c]; *P* = 0.23	
6 hrs after ED arrival	3/48 (6%)	3/46 (7%)	0.81 (0.17 to 3.88)[b]; *P* = 0.79	
Haemoglobin (g/L) arrival at ED	133 (19), 154	118 (23), 152		15 (10 to 19)[d]; *P* = < 0.0001
Calcium (mmol/L) arrival at ED	1.21 (0.42), 152	1.24 (0.37), 156		−0.03 (−0.12 to 0.05)[d]; *P* = 0.44
ROTEM				
EXTEM				
A05 (mm)	35.8 (9.9), 32	33.2 (11.9), 23		2.61 (−3.07 to 8.29)[d]; *P* = 0.37
CFT (seconds)	107 [84.5, 131.5], 32	110 [79, 145], 22		−3 (−36 to 30)[e]; *P* = 0.86
MCF (mm)	55.7 (12.4),32	54.9 (6.01), 20		0.64 (−5.10 to 6.37)[d]; *P* = 0.83
CT (seconds)	78 [73, 107], 33	78 [69, 122], 3		3 (−22 to 28)[c]; *P* = 0.81
α angle (degree)	70 [66, 73], 28	71 [65, 74],23		−1 (−6 to 4)[c]; *P* = 0.67
Ly30 (%)	100 [100, 100], 32	100 [100, 100], 23		0 (−0 to 0)[e]; -
Ly60 (%)	99.5 [99, 100], 22	98.5 [97, 100], 18		1 (−0.29 to 2.29)[c]; *P* = 0.13
FIBTEM				
A05 (mm)	8.73 (3.78), 30	5.86 (2.71), 22		2.89 (1.06 to 4.71)[d]; *P* = 0.0020
CFT (seconds)	76 (-), 1	-		-
MCF (mm)	12.0 (9.6), 29	7.85 (3.34), 20		4.21 (−0.13 to 8.54)[d]; *P* = 0.057
CT (seconds)	73 [67, 101], 31	84 [70, 121], 22		−9 (−33 to 15)[c]; *P* = 0.46
α angle (degree)	63 (7.3), 15	60 (9.0), 7		2.51 (−3.90 to 8.93)[d]; *P* = 0.44

continued

TABLE 11 Further secondary and exploratory outcomes: laboratory results, ROTEM and Multiplate (*continued*)

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
Ly30 (%)	100 [100, 100], 29	100 [100, 100], 22		0 (−0 to 0)[e]; -
Ly60 (%)	100 [100, 100], 21	100 [100, 100], 17		0 (0 to 0)[e]; -
Multiplate				
TRAP	93.4 (49.8), 21	77.6 (44.2), 10		11.0 (−24.2 to 46.2)[d]; *P* = 0.54
ADP	53.5 (40.4), 22	42.8 (24.6), 10		6.36 (−19.7 to 32.4)[d]; *P* = 0.63
ASPI	66.2 (41.8), 21	51.4 (36.5), 10		12.8 (−17.1 to 42.7)[d]; *P* = 0.40

a Output is from a linear regression model adjusted for IDS and the on-scene value of the outcome variable. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.
b Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate lower event rates in the RBC/LyoPlas group.
c Output is from a quantile regression model adjusted for IDS. Values of median differences <0 indicate lower average values in the RBC/LyoPlas group.
d Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.
e Output is from Hodges-Lehmann estimation of the location shift between the two groups and asymptotic CIs. Estimates are not adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.

Note
Data are n/N (%); mean (SD); median [IQR]; or mean (SD), N, or median [IQR], N, when N is different to the total number of participants, unless otherwise specified.
EXTEM, Tissue factor activation; FIBTEM, tissue factor activation + platelet inhibition evaluating the contribution of fibrinogen to clot formation; ROTEM, rotational thromboelastometry.

(95% CI 211 to 1034) ml, adjusted mean difference at 24 hours after hospital arrival 708 (95% CI 180 to 1236) ml]. The number of bags of cryoprecipitate and platelets was similar across all three time points. The volume of colloid was lower in participants in the RBC/LyoPlas group compared to the 0.9% saline group, but the high variability of colloid volume means there is considerable uncertainty associated with these adjusted mean differences.

Further secondary outcomes are summarised in *Table 13*. Acute respiratory distress syndrome (ARDS) was recorded in 9/142 (6%) participants in the RBC/LyoPlas group and 3/129 (2%) in the saline 0.9% group, adjusted relative risk 2.71 (95% CI 0.75 to 9.81). The rate of transfusion-related complications in the first 24 hours after arrival in hospital was similar across the two treatment groups [11/148 (7%) in the RBC/LyoPlas group and 9/137 (7%) in the 0.9% saline group, adjusted risk ratio 1.05 (95% CI 0.46 to 2.42)]. The number of organ failure-free days experienced by participants was similar across treatment groups [mean 12.19 days (SD 13.0) in the RBC/LyoPlas group and 12.1 days (SD 13.1) in the 0.9% saline group, adjusted mean difference 0.86 (95% CI −1.64 to 3.36) days].

Laboratory results, ROTEM and Multiplate are summarised in *Table 11*. Coagulation measured viscoelastically by rotational thromboelastometry (ROTEM©) and platelet function using multiple electrode impedance aggregometry (MultiPlate) data was only collected on participants from selected receiving hospitals. The measurements taken for both sets of EXTEM and FIBTEM tests were similar across treatment group, suggesting that participants in each treatment arm exhibited equivalent coagulation measured viscoelastically profiles. Multiplate data were only collected on 32 participants, and the uncertainty associated with these small sample sizes makes it hard to reach any meaningful conclusions other than that there was an absence of evidence of any meaningful difference between treatment arms.

TABLE 12 Further secondary and exploratory outcomes: blood product usage

Outcome	RBC/LyoPlas	0.9% saline	Adjusted average difference (95% CI)[a]
Total blood product receipt			
RBCs (units)			
6 hrs after arrival at ED	5.61 (5.92), 132	5.31 (5.84), 137	0.09 (−1.27 to 1.45); *P* = 0.89
12 hrs after arrival at ED	6.03 (7.62), 144	5.26 (6.08), 143	0.55 (−1.00 to 2.10); *P* = 0.49
24 hrs after arrival at ED	5.63 (6.14), 139	5.31 (6.33), 134	0.18 (−1.22 to 1.59); *P* = 0.80
Plasma (units)			
6 hrs after arrival at ED	4.31 (4.68), 143	3.97 (4.75), 144	0.16 (−0.90 to 1.22); *P* = 0.77
12 hrs after arrival at ED	4.72 (5.69), 144	4.26 (5.17), 143	0.30 (−0.92 to 1.51); *P* = 0.63
24 hrs after arrival at ED	4.50 (4.76), 139	4.31 (5.40), 134	0.12 (−1.03 to 1.26); *P* = 0.84
Crystalloid (volume)			
6 hrs after arrival at ED	1417 (1610), 142	1037 (1175), 144	382 (61 to 702); *P* = 0.020
12 hrs after arrival at ED	2388 (2031), 143	1782 (1550), 143	628 (221 to 1034); *P* = 0.0025
24 hrs after arrival at ED	3620 (2479), 139	2947 (2115), 134	708 (180 to 1236); *P* = 0.0086
Cryoprecipitate (bags)			
6 hrs after arrival at ED	0.66 (1.23), 143	0.64 (1.38), 144	0.001 (−0.30 to 0.30); *P* = 0.99
12 hrs after arrival at ED	0.89 (1.73), 144	0.80 (1.65), 143	0.05 (−0.33 to 0.43); *P* = 0.79
24 hrs after arrival at ED	0.96 (2.03), 139	0.88 (2.00), 134	0.06 (−0.41 to 0.52); *P* = 0.82
Platelets (bags)			
6 hrs after arrival at ED	0.54 (0.97), 143	0.42 (0.87), 144	0.10 (−0.11 to 0.31); *P* = 0.37
12 hrs after arrival at ED	0.63 (1.14), 144	0.55 (1.02), 143	0.06 (−0.18 to 0.31); *P* = 0.62
24 hrs after arrival at ED	0.71 (1.19), 139	0.67 (1.31), 134	0.02 (−0.27 to 0.31); *P* = 0.90
Colloid (volume)			
6 hrs after arrival at ED	28 (155), 142	83 (317), 144	−55 (−113 to 3); *P* = 0.062
12 hrs after arrival at ED	31 (144), 143	128 (499), 142	−98 (−183 to 13); *P* = 0.024
24 hrs after arrival at ED	105 (368), 138	197 (701), 134	−89 (−221 to 43); *P* = 0.18

a Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group

Note
Data are mean (SD), N.

Exploratory outcomes are summarised in *Table 14*. Both the length of stay in ITU and in hospital, recorded from admission to hospital up to a maximum of 30 days, were similar between treatment groups [adjusted mean differences of −0.40 days (95% CI −2.84 to 2.04) and −1.67 days (95% CI −4.31 to 0.97) respectively]. The occurrence of organ failure on at least one day during hospital stay was assessed for each organ system. Around two-thirds of participants experienced organ failure on at least one day in their respiratory, neurological or cardiovascular systems. One in four participants experienced organ failure on at least one day in their renal system, one in eight participants experienced organ failure on at least one day in their coagulation system, and one in 13 experienced organ failure on at least one day in their liver system. Of the 406 participants providing a response, nearly all (97%) received

TABLE 13 Further secondary and exploratory outcomes – ARDS, transfusion complications, organ failure-free days and all-cause mortality

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
ARDS	9/142 (6%)	3/129 (2%)	2.71 (0.75 to 9.81)[a]; *P* = 0.13	
Transfusion-related complications (in first 24 hours in ED)	11/148 (7%)	9/137 (7%)	1.05 (0.46 to 2.42)[a]; *P* = 0.90	
Organ failure-free days[b]	12.9 (13.0), 202	12.1 (13.1), 212		0.86 (−1.64 to 3.36)[c]; *P* = 0.50
All-cause mortality ≤ 3 hrs of randomisation				
Using time of death only	6/171 (4%)	6/168 (4%)	0.94 (0.32 to 2.82)[a]; *P* = 0.92	−0.001 (−0.04 to 0.04)[d]; *P* = 0.98

a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate lower event rates in the RBC/LyoPlas group.
b 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 hospital and will be assumed to be present if the participant has died.
c Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower average values in the RBC/LyoPlas group.
d Output is from a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 lower event rates in the RBC/LyoPlas group.

Note
Data are n/N (%); or mean (SD), N, when N is different to the total number of participants, unless otherwise specified.

an initial dose of TXA, of the 307 participants providing a response, over two-thirds (69%) received a second dose. Rates of surgery in the first 24 hours following admission to hospital were similar in both treatment groups, with the highest rates reported up to 6 hours after arrival at hospital.

Exploratory Bayesian analyses

We decided a priori to include a Bayesian analysis of the primary outcome and its individual components. The rationale for doing so was to directly estimate the probability of a clinically meaningful treatment effect, which is a measurement of direct interest to clinicians.[18]

Following the DMEC and TSC meetings in May and October 2018, the power calculations were reframed in terms of relative risk rather than absolute risk while maintaining the original target sample size of 490. Based on the observed pooled event rate in May 2018 (65%), and allowing for a 10% loss to follow-up rate, 490 participants would provide 80% power to detect a relative risk ratio of 0.82. This effect size was used to inform the sceptical and information prior distributions in the exploratory Bayesian analyses.

Bayesian models were fitted using three different prior distributions: a non-informative prior, a sceptical prior such that the probability of observing a treatment effect at least as large as a relative risk ratio of 0.82 is <5% and an informative prior reflecting current knowledge. For each set of the priors, *Table 15* provides summary statistics (the mean value, and upper and lower 2.5% quantiles) of the primary outcome event rates in each treatment group. Posterior probabilities of primary outcome rates by treatment group were estimated for Bayesian analyses using each of the three priors, encompassing varying assumptions of benefit from RBC/LyoPlas.

Bayesian analysis of the composite primary outcome

For each set of priors, the median risk ratios and associated 95% higher posterior density intervals for the primary outcome are presented in *Table 16*, along with the posterior probabilities that the risk ratio

TABLE 14 Exploratory outcomes

Outcome	RBC/LyoPlas	0.9% saline	Adjusted risk ratio (95% CI)	Adjusted average difference (95% CI)
ITU length of stay (up to day 30)	(*n* = 142)	(*n* = 130)		
Up to discharge from ITU	10.5 (10.2)	10.9 (10.4)		−0.40 (−2.84 to 2.04)[a]
Hospital length of stay (up to day 30)				
Up to discharge from hospital	17.9 (11.4)	19.7 (10.8)		−1.67 (−4.31 to 0.97)[a]
Any organ failure by system during hospital stay (up to day 30) [SOFA ≥3]				
Respiratory	83/118 (70%)	68/113 (60%)	1.16 (0.96 to 1.40)[b]	
Neurological	89/139 (64%)	74/130 (57%)	1.13 (0.93 to 1.37)[b]	
Cardiovascular	95/138 (69%)	80/126 (63%)	1.09 (0.91 to 1.29)[b]	
Liver	13/130 (10%)	6/122 (5%)	2.09 (0.82 to 5.35)[b]	
Coagulation	12/135 (9%)	19/127 (15%)	0.58 (0.29 to 1.14)[b]	
Renal	32/136 (24%)	33/126 (26%)	0.92 (0.61 to 1.40)[b]	
Use of tranexamic acid				
First TXA dose received	186/193 (96%)	208/213 (98%)	0.99 (0.98 to 1.01)[c]	
Second TXA dose received				
On arrival at ED	85/168 (51%)	68/168 (40%)	1.24 (0.97 to 1.56)[b]	
2 hrs after arrival at ED	54/127 (43%)	60/139 (43%)	1.00 (0.76 to 1.31)[b]	
6 hrs after arrival at ED	52/116 (45%)	50/110 (45%)	1.00 (0.77 to 1.32)[b]	
Any second dose received	111/157 (71%)	102/150 (68%)	1.02 (0.89 to 1.17)[b]	
Surgery				
2 hrs after arrival at ED	51/162 (31%)	45/166 (27%)	1.08 (0.78 to 1.49)[b]	
Between 2 and 6 hrs after arrival at ED	60/155 (39%)	49/151 (32%)	1.10 (0.83 to 1.46)[b]	
Between 6 and 12 hrs after arrival at ED	39/152 (26%)	25/148 (17%)	1.54 (0.98 to 2.42)[b]	
Between 12 and 24 hrs after arrival at ED	32/148 (21%)	31/137 (23%)	0.96 (0.62 to 1.49)[b]	

a Output is from a linear regression model adjusted for IDS. Values of mean differences <0 indicate lower length of stay in the RBC/LyoPlas group.
b Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio < 1 indicate lower event rates in the RBC/LyoPlas group.
c Output from Poisson regression with robust standard errors due to lack of convergence using log-binomial regression model. Model adjusted for IDS. Values of risk ratio <1 indicate lower rate of TXA use with RBC/LyoPlas.

TABLE 15 Priors for Bayesian analysis of primary outcome

Prior	Treatment group	Summary statistics for prior distributions: assumed event rate of composite primary outcome		
		2.5%	Mean, %	97.5%
Non-informative	0.9% saline	2.5	50	97.5
	RBC/LyoPlas	2.5	50	97.5
Sceptical	0.9% saline	55.7	66.7	76.8
	RBC/LyoPlas	55.7	66.7	76.8
Informative	0.9% saline	40	70	93.2
	RBC/LyoPlas	19.4	60	92.5

TABLE 16 Bayesian analysis of primary outcome using all recorded 2 hr post-randomisation lactates: risk ratio adjusted for IDS

Composite outcome	RBC/LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median risk ratio	95% HDI	Probability of risk ratio		
						< 1.0, %	< 0.8, %	< 0.7, %
Yes	128 (64%)	136 (65%)	Non-informative	1.01[a]	(0.88–1.16)[a]	43.5	0.1	0
No	71 (36%)	74 (35%)	Sceptical	1.01[a]	(0.87–1.16)[a]	44	0.1	0
Missing	10	13	Informative	1.01[a]	(0.87–1.16)[a]	44	0.1	0

a Output from Bayesian log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.

is <1, 0.8 and 0.7. The results are extremely similar across all three prior specifications, with posterior risk ratios of 1.01 (95% HDI 0.88 to 1.16) estimated for each. These estimates match the frequentist estimate of the adjusted risk ratio: 1.01 (95% CI 0.88 to 1.17). For each analysis the posterior probability that the risk ratio of experiencing either episode mortality or failure to clear lactate was lower in the RBC/LyoPlas group than in the 0.9% saline group which was 44%. The probability that the risk ratio of experiencing either episode mortality or failure to clear lactate was at least 20% lower (risk ratio of <0.8) in the RBC/LyoPlas group than in the 0.9% saline group which was 0.1%.

For each set of priors, the median absolute risk differences and associated 95% higher posterior density intervals for the primary outcome are presented in *Table 17*, along with the posterior probabilities that the absolute risk difference is less than 0, −10% and −20%. The results are consistent across all three prior specifications, with posterior absolute risk differences ranging from 0.6% (95% HDI −7% to 8%) to −0.4% (HDI −9% to 8%). These estimates align with the frequentist estimate of the adjusted absolute risk differences: −0.025% (95% CI −9% to 9%). Across the Bayesian analyses the posterior probability that the absolute risk of experiencing either episode mortality or failure to clear lactate was lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 44.1% to 53.4%. The probability that the absolute risk of experiencing either episode mortality or failure to clear lactate was at least 10 percentage points lower in the RBC/LyoPlas group than in the 0.9% saline group which ranged from 0.3% to 1.6%.

TABLE 17 Bayesian analysis of primary outcome using all recorded 2 hr post-randomisation lactates: absolute risk difference adjusted for IDS

Composite Outcome	RBC/LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median absolute risk difference	95% HDI	Probability of absolute risk difference		
						< 0.0, %	< −0.1, %	< −0.2, %
Yes	128 (64%)	136 (65%)	Non-informative	0.002[a]	(−0.09 to 0.09)[a]	48.2	1.3	0.007
No	71 (36%)	74 (35%)	Sceptical	0.006[a]	(−0.07 to 0.08)[a]	44.1	0.3	0
Missing	10	13	Informative	−0.004[a]	(−0.09 to 0.08)[a]	53.4	1.6	0

a Output from Bayesian binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.

Bayesian analysis of episode mortality

For each set of priors, the median risk ratios and associated 95% higher posterior density intervals for episode mortality are presented in *Table 18*, along with the posterior probabilities that the risk ratio is <1, 0.8 and 0.7. As for the primary outcome analysis, the results are extremely similar across all three prior specifications, with posterior risk ratios for episode mortality of 0.97 (95% HDI 0.77 to 1.17) or 0.97 (95% HDI 0.77 to 1.18) estimated for each. These estimates are consistent with the frequentist estimate of the adjusted risk ratio: 0.97 (95% CI 0.78 to 1.20). For each analysis, the posterior probability that the risk ratio of experiencing episode mortality was lower in the RBC/LyoPlas group than in the 0.9% saline group was between 63% and 64%. The probability that the risk ratio of experiencing episode mortality was at least 20% lower (risk ratio of <0.8) in the RBC/LyoPlas group than in the 0.9% saline group <5% in all three analyses.

For each set of priors, the median absolute risk differences and associated 95% higher posterior density intervals for episode mortality are presented in *Table 19*, along with the posterior probabilities that the absolute risk difference is <0, −10% and −20%. The results are consistent across all three prior specifications, with posterior absolute risk differences ranging from −5% (95% HDI −12% to 3%) to −3% (HDI −12% to 6%). These estimates align with the frequentist estimate of the adjusted absolute risk differences: −3% (95% CI −12% to 7%). Across the Bayesian analyses, the posterior probability that the absolute risk of experiencing episode mortality was lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 71.2% to 88.2%. The probability that the absolute risk of experiencing episode mortality was at least 10 percentage points lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 5.9% to 9.5%.

TABLE 18 Bayesian analysis of episode mortality: risk ratio adjusted for IDS

Episode mortality	RBC/LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median risk ratio	95% HDI	Probability of risk ratio		
						< 1.0, %	< 0.8, %	< 0.7, %
Yes	88 (43%)	99 (45%)	Non-informative	0.97[a]	(0.77–1.18)[a]	63.1	4.2	0.2
No	115 (57%)	119 (55%)	Sceptical	0.97[a]	(0.77–1.17)[a]	63.6	4.6	0.2
Missing	6	5	Informative	0.97[a]	(0.77–1.17)[a]	64.0	4.6	0.2

a Output from Bayesian log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer episode mortality events with RBC/LyoPlas.

TABLE 19 Bayesian analysis of episode mortality: absolute risk difference adjusted for IDS

Episode mortality	RBC/ LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median absolute risk difference	95% HDI	Probability of absolute risk difference		
						< 0.0, %	< −0.1, %	< −0.2, %
Yes	88 (43%)	99 (45%)	Non-informative	−0.03[a]	(−0.12 to 0.06)[a]	71.2	5.9	0.009
No	115 (57%)	119 (55%)	Sceptical	−0.05[a]	(−0.12 to 0.03)[a]	88.2	8.4	0
Missing	6	5	Informative	−0.04[a]	(−0.13 to 0.05)[a]	80.7	9.5	0.013

a Output from Bayesian binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer episode mortality events with RBC/LyoPlas.

TABLE 20 Bayesian analysis of failure to clear lactate: risk ratio adjusted for IDS

Failure to clear lactate	RBC/LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median risk ratio	95% HDI	Probability of risk ratio		
						< 1.0, %	< 0.8, %	<0.7, %
Yes	98 (50%)	113 (55%)	Non-informative	0.94[a]	(0.78–1.13)[a]	73.5	4.3	0.09
No	98 (50%)	93 (45%)	Sceptical	0.94[a]	(0.77–1.12)[a]	74.4	4.4	0.14
Missing	13	17	Informative	0.94[a]	(0.77–1.12)[a]	74.5	4.5	0.12

a Output from Bayesian log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer failures to clear lactate with RBC/LyoPlas.

Bayesian analysis of failure to clear lactate

For each set of priors, the median risk ratios and associated 95% higher posterior density intervals for failure to clear lactate are presented in *Table 20*, along with the posterior probabilities that the risk ratio is <1, 0.8 and 0.7. The results are similar across all three prior specifications, with posterior risk ratios of either 0.94 (95% HDI 0.78 to 1.13) or 0.94 (95% HDI 0.77 to 1.12) estimated for each. These estimates align well with the frequentist estimate of the adjusted risk ratio: 0.94 (95% CI 0.78 to 1.13). Across all three analyses, the posterior probability that the risk ratio of failure to clear lactate was lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 73.5% to 74.5%. The probability that the risk ratio of failure to clear lactate was at least 20% lower (risk ratio of <0.8) in the RBC/LyoPlas group than in the 0.9% saline group ranged from 4.3% to 4.5%.

For each set of priors, the median absolute risk differences and associated 95% higher posterior density intervals for failure to clear lactate are presented in *Table 21*, along with the posterior probabilities that the absolute risk difference is <0, −10% and −20%. The results are consistent across all three prior specifications, with posterior absolute risk differences ranging from −4% (95% HDI −13% to 5%) to −5% (HDI −14% to 4%). These estimates align closely with the frequentist estimate of the adjusted absolute risk differences: −5% (95% CI −14% to 5%). Across the Bayesian analyses, the posterior probability that the absolute risk of failure to clear lactate was lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 81.3% to 86.9%. The probability that the absolute risk of failure to clear lactate was at least 10 percentage points lower in the RBC/LyoPlas group than in the 0.9% saline group ranged from 5.6% to 11.5%.

TABLE 21 Bayesian analysis of failure to clear lactate: absolute risk difference adjusted for IDS

Failure to clear lactate	RBC/LyoPlas (*N* = 209)	0.9% saline (*N* = 223)	Priors	Median absolute risk difference	95% HDI	Probability of absolute risk difference		
						< 0.0, %	< −0.1, %	< −0.2, %
Yes	98 (50%)	113 (55%)	Non-informative	−0.04[a]	(−0.13 to 0.05)[a]	81.3	11.5	0.05
No	98 (50%)	93 (45%)	Sceptical	−0.04[a]	(−0.11 to 0.04)[a]	84.6	5.6	0
Missing	13	17	Informative	−0.05[a]	(−0.14 to 0.04)[a]	86.9	15.3	0.07

a Output from Bayesian binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer failures to clear lactate with RBC/LyoPlas.

Sensitivity analyses

Sensitivity analyses were undertaken for the primary outcome and each component of the primary outcome: episode mortality and failure to clear lactate. For each sensitivity analysis, the adjusted risk ratio and adjusted risk differences are reported.

Sensitivity analyses for primary outcome

The results of the sensitivity analyses for the primary outcome are presented in *Table 22*. The results from the original analyses are included in the first row for reference. All of the results of the sensitivity

TABLE 22 Sensitivity analyses for primary outcome

RBC/LyoPlas	0.9% saline	Sensitivity analysis	Adjusted risk ratio (95% CI); *p*-value	Adjusted risk difference (95% CI); *p*-value
128/199 (64%)	136/210 (65%)	Original analysis	1.01 (0.88 to 1.17)[a]; *P* = 0.86	−0.00025 (−0.09 to 0.09)[b]; *P* = 0.996
77/130 (59%)	87/151 (58%)	Further covariate adjustment	1.02 (0.95 to 1.08)[c]; *P* = 0.63	0.02 (−0.10 to 0.13)[d]; *P* = 0.79
125/192 (65%)	130/203 (64%)	Per-protocol analysis	1.04 (0.90 to 1.20)[a]; *P* = 0.63	0.014 (−0.08 to 0.11)[b]; *P* = 0.76
125/196 (64%)	126/198 (64%)	Secondary per-protocol analysis	1.03 (0.89 to 1.19)[a]; *P* = 0.68	0.012 (−0.08 to 0.11)[b]; *P* = 0.80
95/151 (65%)	103/153 (67%)	Timing of lactate Concentration	0.99 (0.85 to 1.17)[a]; *P* = 0.94	−0.014 (−0.12 to 0.09)[b]; *P* = 0.80
-	-	Missing responses	(0.87 to 1.17)[e]; *P* = 0.90	−0.001 (−0.094 to 0.091)[f]; *P* = 0.98

a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
b Output is 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 RBC/LyoPlas.
c Log-binomial regression failed due to lack of model convergence. Output is from a Poisson regression model with robust standard error adjusted for IDS, age, capillary lactate, cardiac arrest and GCS. Values of risk ratio <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
d Binomial regression with an identity link adjusted for IDS, age, capillary lactate, cardiac arrest and GCS failed due to lack of model convergence. Output is from a binomial regression model with an identity link adjusted only for IDS. Values of absolute risk difference <0 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
e Output is from estimates pooled over 50 imputed datasets, each analysed using a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
f Output is from estimates pooled over 50 imputed datasets, each analysed using a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.

analyses are consistent with the results from the original analyses. There is little evidence that missing data influenced the results of the primary outcome analysis. Restricting the analysis to the participants providing lactate measurements within the allowable time window did not change the interpretation of the trial results. Restricting the analysis to the participants who adhered to their allocated treatment, using both definitions, did not change the trial results. Accounting for other covariates in the analysis reduced the analysis population, but produced estimates of treatment effect that were consistent with those from the primary analysis.

Sensitivity analyses for episode mortality

The results of the sensitivity analyses for episode mortality are presented in *Table 23*. The results from the original analyses are included in the first row for reference. As for the primary outcome analyses, all of the results of the sensitivity analyses are consistent with the results from the original analyses. Imputing missing data returned treatment estimates that were nearly identical to those in the original analysis. Restricting the analysis to the participants that adhered to their allocated treatment, using both definitions, produced estimates of treatment effect that were even closer to the null values, but the overall interpretation of the episode mortality results did not change. Accounting for other covariates in the analysis reduced the analysis population and produced estimates of episode mortality that were slightly higher in the RBC/LyoPlas treatment arm compared to the 0.9% saline arm, but the uncertainty associated with these estimates meant that the results were consistent with those from the original analysis.

Sensitivity analyses for failure to clear lactate

The results of the sensitivity analyses for failure to clear lactate are presented in *Table 24*. The results from the original analyses are included in the first row for reference. As for the primary outcome and episode mortality analyses, all of the results of the sensitivity analyses are consistent with the results from the original analyses. The missing data analyses produced results that are extremely similar to the results of the original analysis. Restricting the analysis to participants providing lactate measurements made little difference to the results and did not change their interpretation. Restricting the analysis to the participants that adhered to their allocated treatment, using both definitions, produced estimates of

TABLE 23 Sensitivity analyses for episode mortality

RBC/LyoPlas	0.9% saline	Sensitivity analysis	Adjusted risk ratio (95% CI); *p*-value	Adjusted risk difference (95% CI); *p*-value
88/203 (43%)	99/218 (45%)	Original analysis	0.97 (0.78 to 1.20)[a]; *P* = 0.75	−0.03 (−0.12 to 0.07)[b]; *P* = 0.57
50/131 (38%)	55/152 (36%)	Further covariate adjustment	1.02 (0.96 to 1.09)[a]; *P* = 0.50	0.01 (−0.10 to 0.12)[c]; *P* = 0.86
85/194 (44%)	94/210 (45%)	Per-protocol analysis	0.99 (0.80 to 1.23)[a]; *P* = 0.93	−0.02 (−0.11 to 0.08)[b]; *P* = 0.73
85/197 (44%)	91/204 (45%)	Secondary per-protocol analysis	0.98 (0.79 to 1.22)[a]; *P* = 0.86	−0.02 (−0.12 to 0.07)[b]; *P* = 0.65
-	-	Missing responses	0.96 (0.78 to 1.19)[d]; *P* = 0.73	−0.03 (−0.12 to 0.07)[e]; *P* = 0.56

a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer episode mortality events with RBC/LyoPlas.
b Output is from a binomial regression model with an identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer episode mortality events with RBC/LyoPlas.
c Binomial regression with an identity link adjusted for IDS, age, capillary lactate, cardiac arrest and GCS failed due to lack of model convergence. Output is from a binomial regression model with an identity link adjusted only for IDS. Values of absolute risk difference <0 indicate fewer episode mortality events with RBC/LyoPlas.
d Output is from estimates pooled over 50 imputed datasets, each analysed using a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer episode mortality events with RBC/LyoPlas.
e Output is from estimates pooled over 50 imputed datasets, each analysed using a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate episode mortality events with RBC/LyoPlas.

TABLE 24 Sensitivity analyses for failure to clear lactate

RBC/LyoPlas	0.9% saline	Sensitivity analysis	Adjusted risk ratio (95% CI); *p*-value	Adjusted risk difference (95% CI); *p*-value
98/196 (50%)	113/198 (55%)	Original analysis	0.94 (0.78 to 1.13)[a]; *P* = 0.52	−0.05 (−0.14 to 0.05)[b]; *P* = 0.35
55/131 (42%)	70/148 (47%)	Further covariate adjustment	0.96 (0.89 to 1.03)[a]; *P* = 0.29	−0.06 (−0.17 to 0.06)[c]; *P* = 0.33
98/190 (52%)	109/200 (55%)	Per-protocol analysis	0.97 (0.81 to 1.17)[a]; *P* = 0.75	−0.03 (−0.13 to 0.07)[b]; *P* = 0.56
98/193 (52%)	105/195 (55%)	Secondary per-protocol analysis	0.97 (0.80 to 1.16)[a]; *P* = 0.71	−0.03 (−0.13 to 0.07)[b]; *P* = 0.50
74/149 (50%)	85/150 (57%)	Timing of lactate concentration	0.92 (0.74 to 1.14)[a]; *P* = 0.45	−0.06 (−0.17 to 0.05)[a]; *P* = 0.29
-	-	Missing responses	0.94 (0.78 to 1.13)[d]; *P* = 0.50	−0.03 (−0.12 to 0.07)[e]; *P* = 0.56

a Output is from a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer failures to clear lactate concentration with the RBC/LyoPlas group.
b Output is from a binomial regression model with an identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer failures to clear lactate concentration with the RBC/LyoPlas group.
c Binomial regression with an identity link adjusted for IDS, age, capillary lactate, cardiac arrest and GCS failed due to lack of model convergence. Output is from a binomial regression model with an identity link adjusted only for IDS. Values of absolute risk difference <0 indicate fewer episode mortality events with RBC/LyoPlas.
d Output is from estimates pooled over 50 imputed datasets, each analysed using a log-binomial regression model adjusted for IDS. Values of risk ratio <1 indicate fewer failures to clear lactate concentration with the RBC/LyoPlas group.
e Output is from estimates pooled over 50 imputed datasets, each analysed using a binomial regression model with identity link adjusted for IDS. Values of absolute risk difference <0 indicate fewer failures to clear lactate concentration with the RBC/LyoPlas group.

treatment effect that were even closer to the null values, but the overall interpretation of the failure to clear lactate results did not change. Accounting for other covariates in the analysis reduced the analysis population and produced lower estimated incidences of failure to clear lactate in each group, but still produced estimates of treatment effect that were consistent with those from the primary analysis.

Subgroup analyses

Subgroup analyses were conducted for the composite primary outcome and for episode mortality.

Subgroups for primary outcome

The results of the pre-specified subgroup analyses for the composite primary outcome are presented in *Table 25*. There was no compelling evidence of any subgroup effect for the primary outcome. Although the incidence rates of the primary outcome varied by IDS, and there was some difference in rates across treatments arms within an IDS, these differences were not enough to conclude that there was a significant difference in treatment effect between IDS. There was little evidence that the estimated risk ratios for the composite primary outcome varied by IDS.

The results of two additional post-hoc subgroup analyses are presented in *Table 26*. One subgroup analysis examined the association between the primary outcome and band of injury severity score (NISS < 16 vs. 16 to 30 vs. > 30) and the other examined the association between the primary outcome and transport time from scene to hospital (<20 minutes vs. ≥20 minutes). As with the pre-specified subgroup analyses, there was no compelling evidence of any subgroup effect for the primary outcome in these post-hoc analyses.

TABLE 25 Subgroup analyses for the primary outcome

Subgroup description	RBC/LyoPlas (*N* = 199) (%)	0.9% saline (*N* = 210)	Adjusted risk ratio (95% CI)	*p*-value for interaction
IDS				
Site 1	49/67 (73)	43/63 (68)	1.07 (0.86 to 1.34)[a]	0.28
Site 2	26/33 (79)	24/37 (65)	1.21 (0.90 to 1.63)[a]	
Site 3	31/58 (53)	36/57 (63)	0.85 (0.62 to 1.16)[a]	
Site 4	22/41 (54)	33/53 (62)	0.86 (0.61 to 1.23)[a]	
Mode of transport				
Air	49/76 (64)	53/80 (66)	0.98 (0.79 to 1.23)[a]	0.74
Ground	79/123 (64)	83/130 (64)	1.03 (0.86 to 1.24)[a]	
Initial lactate concentration				
≤2.2 mmol/L	3/3 (100)	1/1 (100)	1.05 (0.99 to 1.13)[b]	0.36
>2.2 mmol/L	120/190 (63)	126/199 (63)	1.00 (0.94 to 1.06)[b]	
Cardiac arrest				
Yes	20/21 (95)	20/20 (100)	0.96 (0.91 to 1.01)[b]	0.32
No	70/123 (57)	82/147 (56)	1.01 (0.93 to 1.09)[b]	
Time to ED from injury				
≤1 hour	19/34 (56)	15/30 (50)	1.18 (0.74 to 1.86)[a]	0.47
>1 hour	74/128 (58)	80/135 (59)	0.98 (0.80 to 1.19)[a]	
Mode of injury				
Blunt	101/147 (69)	112/163 (69)	1.00 (0.94 to 1.06)[b]	0.83
Penetrating	24/43 (56)	23/43 (53)	1.02 (0.89 to 1.17)[b]	
Crush	0/2 (0)	0/0 (-)	-	
Multiple modes	3/7 (43)	1/4 (25)	1.11 (0.73 to 1.67)[b]	
Volume of pre-hospital fluid given				
4 units	55/80 (69)	56/73 (77)	0.93 (0.77, 1.13)[a]	0.35
<4 units	73/118 (62)	80/137 (58)	1.06 (0.87 to 1.29)[a]	
Age				
<50 years	72/124 (58)	74/124 (60)	0.99 (0.81 to 1.22)[a]	0.58
50 – 70 years	30/44 (68)	35/56 (63)	1.09 (0.82 to 1.45)[a]	
>70 years	13/18 (72)	16/19 (84)	0.87 (0.60 to 1.25)[a]	
Head injury[c]				
Positive	2/2 (100)	5/6 (83)	1.06 (0.90 to 1.24)[b]	0.97
Negative	38/58 (66)	33/58 (57)	1.06 (0.95 to 1.18)[b]	
Compressible haemorrhage				
Compressible haemorrhage	20/37 (54)	18/35 (51)	1.07 (0.69 to 1.65)[a]	0.27

TABLE 25 Subgroup analyses for the primary outcome (*continued*)

Subgroup description	RBC/LyoPlas (*N* = 199) (%)	0.9% saline (*N* = 210)	Adjusted risk ratio (95% CI)	*p*-value for interaction
Non-compressible haemorrhage	98/149 (66)	113/164 (69)	0.97 (0.83 to 1.14)[a]	
Both types of haemorrhage	10/13 (77)	5/11 (45)	1.67 (0.82 to 3.39)[a]	
Pre-morbid drug history[d]				
Anticoagulant/antiplatelet medication	11/17 (65)	10/24 (42)	1.16 (0.96 to 1.42)[b]	0.42
No anticoagulant/ antiplatelet medication	59/120 (49)	49/99 (49)	1.00 (0.92 to 1.10)[b]	
Unknown anticoagulant/ antiplatelet medication	27/29 (93)	34/41 (83)	1.04 (0.96 to 1.13)[b]	
Age of blood products[e]				
<8 days	11/14 (79)	-		
≥8 days	113/179 (63)	-		

a Output from log-binomial regression model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
b Output from Poisson regression with robust standard errors due to lack of convergence using log-binomial regression model. Model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
c Head injury data was only collected since 29 August 2019, hence only 124 participants provided both head injury and primary outcome data.
d Premorbid drug history was collected on the medical history case report form (CRF), which was only completed by 342 participants. Hence, this subgroup analysis only includes the 330 participants who provided primary outcome data and completed the medical history CRF.
e Age of blood products can only be calculated for participants allocated to the RBC/LyoPlas treatment arm, hence there can be no treatment comparisons within these groups.

Subgroups for episode mortality

The results of the pre-specified subgroup analyses for episode mortality are presented in *Table 27*. There was no strong evidence of any subgroup effect for episode mortality, although two subgroup analyses did suggest a possible subgroup effect. Similar to the findings for the primary outcome, the incidence rates of episode mortality varied by IDS, and there was some difference in rates across treatments arms within an IDS. Estimated treatment effects varied from 0.55 (95% CI 0.31 to 0.99) to 1.42 (95% CI 0.89 to 2.27) by IDS, but these differences were not large enough to conclude that there was a significant difference in treatment effect between IDS. The subgroup analysis examining premorbid drug history suggests that participants receiving either anticoagulant or antiplatelet medication may experience a higher rate of episode mortality if allocated to RBC/LyoPlas compared to 0.9% saline. This treatment effect is higher than in participants known to be receiving neither anticoagulant nor antiplatelet medication and in participants with unknown history of anticoagulant or antiplatelet medication. However, this analysis is based on small numbers of episode mortality events in the participants receiving either anticoagulant or antiplatelet medication, and the initial regression model experiences convergence problems. Hence, this result should be interpreted with caution.

TABLE 26 Post-hoc subgroup analyses for the primary outcome

Subgroup description	RBC/LyoPlas (*N* = 50) (%)	0.9% saline (*N* = 54) (%)	Adjusted risk ratio (95% CI)	*p*-value for interaction
NISS band				
<16	1/7 (14)	1/7 (14)	0.95 (0.07 to 12.30)[a]	0.82
16 to 30	11/26 (42)	8/24 (33)	1.32 (0.64, 2.70)[a]	
> 30	68/107 (64)	69/111 (62)	1.04 (0.86, 1.27)[a]	
Transport time: Time to ED from leaving scene				
<20 minutes	12/17 (71)	8/15 (53)	1.12 (0.91, 1.37)[b]	0.64
≥20 minutes	20/33 (61)	22/39 (56)	1.05 (0.91, 1.22)[b]	

a Output from log-binomial regression model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.
b Output from Poisson regression with robust standard errors due to lack of convergence using log-binomial regression model. Model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of negative events (episode mortality or failure to clear lactate concentration) with RBC/LyoPlas.

TABLE 27 Subgroup analyses for episode mortality

Subgroup description	RBC/LyoPlas (*N* = 199) (%)	0.9% saline (*N* = 210) (%)	Adjusted risk ratio (95% CI)	*p*-value for interaction
IDS				
Site 1	33/67 (49)	30/64 (47)	1.05 (0.74 to 1.50)[a]	0.07
Site 2	21/36 (58)	16/39 (41)	1.42 (0.89 to 2.27)[a]	
Site 3	23/58 (40)	27/60 (45)	0.88 (0.58 to 1.35)[a]	
Site 4	11/42 (26)	26/55 (47)	0.55 (0.31 to 0.99)[a]	
Mode of transport				
Air	40/77 (52)	41/84 (49)	1.07 (0.79 to 1.44)[a]	0.41
Ground	48/126 (38)	58/134 (43)	0.89 (0.67 to 1.20)[a]	
Initial lactate concentration				
≤2.2 mmol/L	1/4 (25)	0/1 (0)	1.30 (0.93 to 1.83)[b]	0.35
>2.2 mmol/L	82/190 (43)	90/201 (45)	0.99 (0.92 to 1.06)[b]	
Cardiac arrest				
Yes	20/21 (95)	20/20 (100)	0.97 (0.92 to 1.02)[b]	0.49
No	43/126 (34)	50/151 (33)	1.01 (0.93 to 1.09)[b]	
Time to ED from injury				
≤1 hour	9/33 (27)	11/30 (37)	0.75 (0.36 to 1.55)[a]	0.45
>1 hour	46/133 (35)	47/140 (34)	1.02 (0.74 to 1.41)[a]	
Mode of injury				
Blunt	73/151 (48)	79/169 (47)	1.01 (0.93 to 1.08)[b]	0.14
Penetrating	13/43 (30)	20/44 (45)	0.90 (0.78 to 1.04)[b]	
Crush	0/2 (0)	0/0 (-)	-	
Multiple modes	2/7 (29)	0/5 (0)	1.26 (0.98 to 1.62)[b]	

TABLE 27 Subgroup analyses for episode mortality (*continued*)

Subgroup description	RBC/LyoPlas (*N* = 199) (%)	0.9% saline (*N* = 210) (%)	Adjusted risk ratio (95% CI)	*p*-value for interaction
Volume of pre-hospital fluid given				
4 units	41/80 (51)	42/76 (55)	0.95 (0.71 to 1.28)[a]	0.96
<4 units	47/122 (39)	57/142 (40)	0.96 (0.71 to 1.30)[a]	
Age				
<50 years	41/124 (33)	54/129 (42)	0.80 (0.58 to 1.10)[a]	0.29
50–70 years	21/46 (46)	21/56 (38)	1.24 (0.78 to 1.96)[a]	
>70 years	13/20 (65)	13/22 (59)	1.05 (0.64 to 1.72)[a]	
Head injury[c]				
Positive	2/2 (100)	2/6 (33)	1.46 (1.10 to 1.93)[b]	0.13
Negative	26/58 (45)	22/62 (35)	1.06 (0.94 to 1.21)[b]	
Compressible haemorrhage				
Compressible haemorrhage	9/37 (24)	13/37 (35)	0.72 (0.35 to 1.47)[a]	0.08
Non-compressible haemorrhage	72/153 (47)	84/169 (50)	0.95 (0.76 to 1.19)[a]	
Both types of haemorrhage	7/13 (54)	2/12 (17)	3.32 (0.85 to 12.94)[a]	
Pre-morbid drug history[d]				
Anticoagulant/ antiplatelet medication	7/19 (37)	0/26 (0)	1.36 (1.16 to 1.60)[b]	0.01
No anticoagulant/ antiplatelet medication	26/121 (21)	26/102 (25)	0.97 (0.88 to 1.06)[b]	
Unknown anticoagulant/ antiplatelet medication	25/29 (86)	30/41 (73)	1.07 (0.97 to 1.19)[b]	
Age of blood products[e]				
<8 days	6/14 (43)	-		
≥8 days	78/182 (43)	-		

a Output from log-binomial regression model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of episode mortality with RBC/LyoPlas.
b Output from Poisson regression with robust standard errors due to lack of convergence using log-binomial regression model. Model adjusted for treatment group, IDS, subgroup variable, and the interaction between treatment group and subgroup variable. Values of risk ratio <1 indicate lower rate of episode mortality with RBC/LyoPlas.
c Head injury data was only collected since 29 August 2019, hence only 124 participants provided both head injury and primary outcome data.
d Premorbid drug history was collected on the medical history CRF, which was only completed by 342 participants. Hence, this subgroup analysis only includes the 330 participants who provided primary outcome data and completed the medical history CRF.
e Age of blood products can only be calculated for participants allocated to the RBC/LyoPlas treatment arm, hence there can be no treatment comparisons within these groups.

Safety outcomes

The rates of complications and adverse events by treatment group are reported in *Table 28*. There was only one reported transfusion-related acute lung injury, and rates of thromboembolism were similar across the treatment groups. There was the suspicion or clinical evidence of infection in 65% of participants who completed at least one in-hospital daily assessment. This rate was similar across both treatment groups. There were only two serious adverse events recorded in the RePHILL trial. There were no required dose reductions during the trial, and no participants needed to have their trial treatment discontinued for drug-related toxicity. None of the deaths in the RePHILL study were related to the trial treatments.

TABLE 28 Complications and adverse events by group

	RBC/LyoPlas (*n* = 142)	0.9% saline (*n* = 130)
Transfusion-related acute lung injury		
Yes	0/142 (0%)	1/130 (1%)
No	142/142 (100%)	128/130 (99%)
Missing	0/140	1/130
Thromboembolism		
Yes	17/142 (12%)	11/130 (8%)
No	125/142 (88%)	118/130 (91%)
Missing	0/142 (0%)	1/130 (1%)
Type of thromboembolism[a]		
Deep vein thrombosis	3/142 (2%)	3/130 (2%)
Pulmonary embolism	9/142 (6%)	8/130 (6%)
Stroke	3/142 (2%)	0/130 (0%)
Other	2/142 (1%)	3/130 (2%)
Suspicion or clinical evidence of infection	(*n* = 142)	(*n* = 130)
Yes (%)	92/142 (65%)	83/130 (64%)
No (%)	50/142 (35%)	47/130 (36%)
Missing	0/142 (0%)	0/130 (0%)
Type of infection[a]		
Intra-abdominal	26/142 (18%)	15/130 (12%)
Meningitis	3/142 (2%)	1/130 (1%)
Respiratory	61/142 (43%)	59/130 (45%)
Urinary tract infection	5/142 (4%)	10/130 (8%)
Soft tissue	35/142 (25%)	20/130 (15%)
Indwelling device	16/142 (11%)	13/130 (10%)
Blood-borne	8/142 (6%)	7/130 (5%)
Other	46/142 (32%)	40/130 (31%)

a Multiple responses are possible for the type of thromboembolism and type of infection.

Note
Data are n/N (%). This list of adverse events and complications is for the 272 participants that completed at least one daily assessment form.

Blood product wastage

RBC and LyoPlas wastage was measured at two of the trial blood banks. In total, 2496 RBC units were issued, 171 units were administered to patients, 2325 units were returned to blood bank stock and 53 units required disposal. This equates to a wastage rate of 2.12%. Amongst 2496 units of LyoPlas that were issued, 31 were wasted, equating to a rate of 1.24%.

Good clinical practice of compliance statement

The trial was run in accordance with the requirements of Good Clinical Practice. No serious breaches occurred during the conduct of the trial.

Chapter 4 Discussion

The RePHILL prospective multi-centre randomised controlled superiority trial recruited 432 patients with trauma-related haemorrhagic shock in a civilian setting. For the primary outcome, a composite of episode mortality and lactate clearance, the trial did not demonstrate that pre-hospital RBC/LyoPlas resuscitation was superior to 0.9% sodium chloride. Participants' vital signs (heart rate, blood pressures, respiratory rate, oxygen saturations), markers of shock (lactate) and coagulopathy were similar between groups at hospital arrival. Participants randomised to the RBC/LyoPlas group had a higher haemoglobin on admission to hospital and received cumulatively more blood products in total than those in the control group.

Although the point estimates for the individual components of the primary outcome and some other secondary outcomes (early survival) are consistent with a benefit from allocation to RBC/LyoPlas, the CIs are wide and include the possibility of both benefits and harms. The Bayesian exploratory analysis allowed the trial to examine the composite primary outcome and its individual components across a range of prior beliefs about the effectiveness of blood/LyoPlas. For the composite primary outcome, the probability that RBC/LyoPlas was superior (i.e. an absolute risk difference >0) compared to 0.9% saline was between 44.1 and 53.%. For episode mortality, the probability was 71.2 to 88.2% and for lactate clearance 81.3 to 86.9%. However, the 95% credible intervals crossed zero, included the possibility for benefit as well as harm.

The use of PHBP for haemorrhagic shock following major trauma has been driven by the desire to deliver earlier in the patient pathway interventions traditionally reserved until hospital arrival. Research in both military and civilian settings suggests that early transfusion improves survival although the evidence from randomised trials remains inconclusive.[10] Trials involving pre-hospital plasma have produced conflicting results. The Pre-hospital Air Medical Plasma (PAMPer) clinical trial showed a nearly 30% relative reduction in mortality with plasma transfusion in the pre-hospital environment (30 day mortality 23.2% vs. 33.0%).[8] In contrast the Control of Major Bleeding After Trauma Trial (COMBAT) trial which randomised adults with haemorrhagic shock to pre-hospital plasma or saline was stopped after enrolment of 144/150 participants due to futility (28 day mortality was 15% in the plasma group vs. 10% in the control group). The Pre-hospital Administration of Lyophilized Plasma for Post-traumatic Coagulopathy Treatment (PREHO-PLYO) trial randomised 150 participants with major trauma to 4 LyoPlas units or 0.9% saline. The study found no difference in the primary outcome [INR on arrival at the hospital or in 30-day survival (17.6% plasma group vs. 15.2%), OR 1.20 (0.43 to 3.37)].[19]

It is worth considering why the present study did not find clear benefit from PHBP. First, the study took place in a civilian setting within an established major trauma network. Pre-hospital critical care is provided at the scene of the incident by specialist doctors and critical care paramedics, who already bring forward some of the advanced life support treatments traditionally delayed until hospital arrival. Second, the national trauma network has been configured to facilitate transfer to a major trauma centre within 60 minutes of injury.[20] Although the overall time from scene to arrival at the ED was on average median 57 (IQR 40 to 78) minutes, a third of participants with recorded transport times (from scene to ED) had an interval of less than 20 minutes. Whilst our subgroup analysis did not find evidence of an interaction based on transport time, a larger, post-hoc analysis of the PAMPer and COMBAT trials reported that the survival benefit from pre-hospital transfusion was limited to patients who had transport times of less than 20 minutes.[21] Third, due to the logistical challenges created by the limited post-thaw shelf life of fresh frozen plasma at the time of the study, RePHILL used freeze-dried (LyoPlas). This decision was based on evidence that LyoPlas has similar or improved biological efficacy relative to fresh frozen plasma.[22,23] However, a secondary, non-randomised analysis of the PAMPer trial showed that compared with crystalloid only resuscitation, resuscitation with fresh frozen plasma in combination with red cells reduced 30 day mortality (37% vs. 26%, $P = 0.05$).[24] The authors however highlight that

their findings could be limited by residual confounding. Further research is required to determine if the apparent differences were due to the use of LyoPlas or fresh frozen plasma. Fourthly, RePHILL used a red cell to plasma ratio of 1 : 1 consistent with UK national guidelines for major haemorrhage.[20] Whether different ratios, the addition of platelets, coagulation factors or administration of whole blood would have made a difference remains to be determined by future research. Finally, the population of civilian participants enrolled in RePHILL were older, more severely injured and had a higher proportion of blunt traumatic injuries than in observational military studies which have suggested benefit from pre-hospital blood transfusion.[25,26] Although the subgroup analysis according to injury severity scores (<16, 16 to 30 or ≥ 30) did not find evidence of interaction, it remains possible that some patients were too well or too sick to benefit from treatment with blood and plasma.

Part of the hypothesis for the putative benefits of transfusing red cells relate to early optimisation of oxygen delivery to the tissues. Guidelines recommend red cell transfusion when the level of haemoglobin falls below 70–90 g/L, except in older patients and those with traumatic brain injury who may benefit from higher concentrations of Hb.[27] Despite observing higher haemoglobin levels on admission to hospital [133 (SD 19) in the RBC/LyoPlas group compared with 118 (SD 23) in the saline group], RePHILL did not find evidence that pre-hospital transfusion improved oxygen delivery as measured by lactate level or the rate of lactate clearance. This may in part be explained by only a small proportion of participants (9/152, 6%) in the 0.9% saline group arriving at hospital with a haemoglobin <80, highlighting the difficulty in identifying patients in the pre-hospital setting who are anaemic at the time of assessment.

Blood and blood components are a scarce resource. Substantial efforts are therefore put into the supply chain to minimise wastage. This is particularly important when using O negative blood as demand for O negative RBCs is 12% in the UK, but this group makes up only 8% of the population.[28] Data from the National Blood and Transplant Service during the conduct of the trial indicates that blood product wastage occurred in 2.5% of units issued for red cells (4.7% for group O negative blood).[29] Given the environmental challenges inherent with the delivery of care in the pre-hospital environment, when extending transfusion operations into that setting it is important to take care to minimise wastage. In a prospective observational study, in the context of a quality improvement initiative, the London Air Ambulance explored blood wastage related to the supply of whole blood.[30] Over a two-year period, which involved four Plan-Do-Study-Act cycles, mean weekly wastage reduced from 8.36 units (70%) to 3.19 units (27%). Although not directly comparable (as the shelf life for whole blood is 14 days compared to 35 days for RBCs), the low wastage seen in the RePHILL trial (2%) provides assurance that the use of pre-hospital RBCs does not lead to substantial wastage. However, the finding that those in the pre-hospital transfusion group not only received earlier blood but also had higher total blood product usage, without definitive evidence of benefit, suggests the need for more careful assessment of transfusion requirements in hospital in those who received pre-hospital blood.

Equality, diversity and inclusion

Given the unpredictable nature of life-threatening haemorrhagic shock and the need for emergency treatment, it was not possible for us to take active steps to enrich the diversity of the population of patients recruited. However, the population enrolled broadly reflected the ethnicity characteristics of England and Wales (www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest, accessed 6 July 2022). The study protocol excluded people with a known objection to blood or blood product transfusion in order to respect the individual's rights to accept or refuse treatment. We also excluded women who were known or suspected to be pregnant due to the potential greater transfusion risks in this population. Finally, we excluded prisoners due to the perceived difficulty of obtaining follow-up data for this population. In

subsequent research, we have shown that it is feasible to obtain survival outcomes data for this group of patients through the Office for National Statistics.[31]

Strengths and limitations

RePHILL is the first RCT to evaluate the clinical effectiveness of pre-hospital blood transfusion. The trial overcame substantial regulatory, supply and logistical challenges. It is the first to engage multiple air ambulance charities in a randomised clinical trial of an investigational medicinal product. The case mix of participants enrolled were typical of UK civilian major trauma. The injury severity scores confirm that the group of participants enrolled had, as anticipated, severe injuries. These findings support the generalisability of the research findings to the UK civilian trauma population.

Alongside these strengths, the trial also has limitations. First, we recruited only 88% of our planned sample size due to the impact of COVID-19 and the withdrawal of several air ambulance partners. Given the similarity of the primary and secondary outcomes between the intervention and control group, although it is possible that not recruiting the full sample size may have led to a type 2 error, we consider it unlikely that it would have led to a substantively different finding. This position is further supported by simulations examining the effect of large increases in sample sizes which would not have materially altered the findings for the primary outcome. Whether a larger trial would have influenced the secondary outcomes, remains to be determined in future studies.

COVID-19 had a global impact on clinical trials leading to thousands of clinical trials closing prior to reaching the intended sample size.[32] The CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) statement provides guidance to help improve the transparency, quality and completeness of reporting.[33] Adopting that framework in the context of RePHILL can be summarised as:

- Extenuating circumstance: (1) COVID-19 led to an inability to maintain safe oversight for the trial due to a combination sickness and redeployment of clinical and research staff. (2) National lockdowns reduced the incidence of major trauma.
- Impact: (1) Sponsor paused trial recruitment (March 2020 through to July 2020). (2) Fewer cases of major trauma leading to lower recruitment rates. Together these meant that the study fell short of reaching the intended sample size.
- Mitigations: Recruitment window extended; addition of Bayesian analysis.
- These are important modifications as they reduced the statistical power of the study.

Although multi-centre RCTs are considered the gold standard of evidence, it takes considerable time to design and recruit sufficient numbers. Other pre-hospital transfusion trials have faced challenges – with the Control of Major Bleeding After Trauma – COMBAT stopped prematurely due to futility[9] and the Pre-Hospital Use of Plasma for Traumatic Hemorrhage – PUPTH due to insufficient recruitment.[34] The withdrawal of several air ambulance services prior to the start of the trial also adversely affected delivering the trial on time and target. The clinical and commercial pressures for early adoption (www.londonsairambulance.org.uk/news-and-stories/charity/uks-first-air-ambulance-to-carry-blood-on-board, accessed 25 February 2022)[35,36] and loss of equipoise[37] meant that early evaluations of pre-hospital blood were limited to observational studies[38,39] and reduced the pool willing to participate in a randomised evaluation. Future randomised studies will need to carefully consider the pressures for early adoption inherent in this sector and work carefully with air ambulance partners to agree future research priorities.

Research in trauma-related haemorrhagic shock is limited by the absence of a core outcome set. A systematic review examining outcome measures used in clinical research evaluating pre-hospital

blood component transfusion in traumatically injured bleeding patients identified over 212 outcome measures across 34 studies,[40] highlighting significant heterogeneity in outcomes across previous trials. A composite primary outcome reflecting the efficacy of initial resuscitation (lactate clearance) and overall effectiveness (death) was chosen after careful consideration by the trial investigators, funders and patient and public involvement groups. Despite the empirical attractiveness to this composite outcome, the direction of effects observed in RePHILL for mortality −3% (−12% to 7%) and improved lactate clearance −5% (−14% to 5%) do not appear to have been additive when combined as a composite outcome [i.e. negligible difference seen in the composite outcome −0.025% (−9% to 9%)]. This could be explained by the most seriously injured patients, at highest risk of early death, would also have high lactate loads. An effective treatment that averted early death could be mitigated by producing a survivor with impaired lactate clearance. This suggests investigators should be cautious about its use in future studies.

Given the nature of the intervention and the setting for administration, it was not possible to mask treatment allocation to those delivering the intervention. It is possible that this may have led to performance bias during both the pre-hospital and ED treatment of enrolled patients. The key trial outcomes were objective measurements and thus it was unlikely that they were influenced by knowledge of treatment assignment. More subjective measures (e.g. transfusion reactions, adverse events) may have been more susceptible to detection bias.

Future research

There remains an urgent need to develop evidence-based interventions to improve outcomes from haemorrhagic shock secondary to acute traumatic injuries.

A key challenge is to identify the population of patients most likely to benefit from pre-hospital interventions.[41] The RePHILL trial recruited a population of severely injured patients characterised by high injury severity scores and overall high episode mortality.[42] By contrast, the COMBAT trial recruited less severely injured patients (and had a short time between intervention and hospital arrival) and similarly did not find evidence of benefit from up to two units of thawed plasma.[9] The PAMPer trial,[8] the only trial to find a benefit from pre-hospital transfusion (of up to two units of plasma) recruited a group of moderately injured patients who were on average 42 minutes from away from definitive hospital-delivered treatments. This suggests there may be an optimal set of inclusion/exclusion criteria for recruitment to future trials which avoids recruiting those unlikely to benefit from having either catastrophic injury (e.g. traumatic cardiac arrest) or least severe injuries who are likely to survive irrespective of pre-hospital transfusions. However, there remains a key challenge to identify this population of patients at the roadside. Whilst some post-hoc analyses (e.g. longer pre-hospital transport time, CT evidence of brain injury) suggest there may be subgroups with better outcomes, none of the a priori subgroup analyses across the three trials, which can be assessed at the point of injury, demonstrated evidence of benefit. Further research is required to identify the characteristics of patients most likely to benefit from pre-hospital transfusion.

The discordant findings from the four prior randomised transfusion trials highlight the need for further research to identify the optimal intervention(s) in trauma-related haemorrhagic shock.[8,9,19,42,43] Consideration should be given to both the components transfused, and the sequence and dose. Such research should be informed by the findings (once published) of the Pre-hospital Plasma or Red Blood Cell Transfusion Strategy in Major Bleeding (PRIEST; www.clinicaltrials.gov/ct2/show/NCT04879485, accessed 28 September 2022).[44] The role of whole blood, which reduces the need for transfusing individual components, showed promise in a single-centre pilot randomised trial[45] and is being explored in the Type O Whole Blood and Assessment of Age During Pre-hospital Resuscitation Trial (TOWAR; https://clinicaltrials.gov/ct2/show/NCT04684719, accessed 28 September 2022)[46] and Study of

Whole Blood In Frontline Trauma (SWIFT; www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/swift/trial, accessed 28 September 2022).[47] Noting that early treatment is critical for best outcomes in traumatic haemorrhage,[48,49] future trials will need to consider how to enable interventions to be delivered earlier in the patient pathway.

A systematic review of outcome measures used in clinical research evaluating pre-hospital blood component transfusion patients with trauma-related haemorrhagic shock identified substantial heterogeneity in the outcomes reported. Many outcomes focused on evidence of clinical effectiveness with limited insights provided into safety and complications.[40] The absence of a core outcome set for pre-hospital transfusion trials presents a significant challenge for researchers seeking to identify the optimal outcomes for individual trials and to facilitate meta-analyses between trials. The Core Outcomes Set for Cardiac Arrest (COSCA) includes survival to hospital discharge (or 30 days), survival with a favourable neurological outcome and health-related quality of life.[50] While survival to and beyond hospital discharge may be desirable for large effectiveness trials, any treatment effect from pre-hospital transfusion will likely be diluted due to severity of underlying injuries and treatments administered after hospital arrival. Future trials that wish to demonstrate evidence of efficacy may need to focus on outcomes earlier in the patient journey such as survival to hospital admission or within the first 24 hours of injury. Further research and consensus work is needed to define the optimal outcomes set for efficacy and effectiveness trials, what constitutes the minimal clinically important differences for these outcomes and what the optimal experimental designs are to answer the specific research questions.[18]

Chapter 5 Conclusions

This multi-centre, allocation concealed, open-label, parallel group RCT in participants with trauma-related haemorrhagic shock did not demonstrate that pre-hospital RBC/LyoPlas was superior to 0.9% saline for the composite outcome of episode mortality and/or lactate clearance.

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Ethics statement

The study was approved by South Central Research Ethics Committee (15/SC/0691) on 15 December 2015.

Data-sharing statement

Requests for access to data from the RePHILL trial should be addressed to the corresponding author at rephill@trials.bham.ac.uk. The individual participant data collected during the trial (including the data dictionary) will be available, after de-identification, with no end date. All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the trial management group before data release.

References

1. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;**376**(9734):23–32.
2. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, *et al.*; PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013;**148**(2):127–36.
3. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;**22**(7):707–10.
4. Morrison JJ, Oh J, DuBose JJ, O'Reilly DJ, Russell RJ, Blackbourne LH, *et al.* En-route care capability from point of injury impacts mortality after severe wartime injury. *Ann Surg* 2013;**257**(2):330–4.
5. Bailey JA, Morrison JJ, Rasmussen TE. Military trauma system in Afghanistan: lessons for civil systems? *Curr Opin Crit Care* 2013;**19**(6):569–77.
6. O'Reilly DJ, Morrison JJ, Jansen JO, Apodaca AN, Rasmussen TE, Midwinter MJ. Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study. *J Trauma Acute Care* 2014;**77**:S114–20.
7. Smith IM, James RH, Dretzke J, Midwinter MJ. Prehospital blood product resuscitation for trauma: a systematic review. *Shock* 2016;**46**(1):3–16.
8. Sperry JL, Guyette FX, Brown JB, Adams PW. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *New Engl J Med* 2018;**379**(4):315–26.
9. Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, *et al.* Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet* 2018;**392**(10144):283–91.
10. van Turenhout EC, Bossers SM, Loer SA, Giannakopoulos GF, Schwarte LA, Schober P. Prehospital transfusion of red blood cells. Part 2: a systematic review of treatment effects on outcomes. *Transfusion Med* 2020;**30**(2):106–33.
11. DeBot M, Sauaia A, Schaid T, Moore EE. Trauma-induced hypocalcemia. *Transfusion* 2022;**62**:274–80.
12. Jenkins D, Stubbs J, Williams S, Berns K, Zielinski M, Strandenes G, Zietlow S. Implementation and execution of civilian remote damage control resuscitation programs. *Shock* 2014;**41**(Suppl. 1):84–9.
13. Jenkins DH, Rappold JF, Badloe JF, Berséus O, Blackbourne L, Brohi KH, *et al.* Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. *Shock* 2014;**41**:3–12.
14. Smith IM, Crombie N, Bishop JR, *et al.* RePHILL: protocol for a randomised controlled trial of pre-hospital blood product resuscitation for trauma. *Transfusion Med* 2018;**28**(5):346–56.
15. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, *et al.* Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochr Datab Syst Rev* 2012;**11**:MR00030.

16. Régnier MA, Raux M, Le Manach Y, Asencio Y, Gaillard J, Devilliers C, *et al.* Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology* 2012;**117**(6):1276–88.

17. Chase JG, Pretty CG, Pfeifer L, Shaw GM, Preiser J-C, Le Compte AJ, *et al.* Organ failure and tight glycemic control in the SPRINT study. *Crit Care* 2010;**14**(4):R154.

18. Yarnell CJ, Darryl A, Baldwin MR, Brodie D, Fan E, Ferguson ND, *et al.* Clinical trials in critical care: can a Bayesian approach enhance clinical and scientific decision making? *Lancet Respir Med* 2021;**9**:207–16.

19. Jost D, Lemoine L, Lemoine F, Derkenne C, Beaume S, Lanoë V, *et al.* Prehospital lyophilized plasma transfusion for trauma-induced coagulopathy in patients at risk for hemorrhagic shock: a randomized clinical trial. *JAMA Netw Open* 2022;**5**:e2223619.

20. National Institute for Health and Care Excellence. *Major Trauma: Assessment and Initial Management NICE Guideline* [NG39]. 2016. URL: www.nice.org.uk/guidance/ng39 (accessed 21 December 2021).

21. Pusateri AE, Moore EE, Moore HB, Le TD, Guyette FX, Chapman MP, *et al.* Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials. *JAMA Surg* 2020;**155**(2):e195085.

22. Bux J, Dickhorner D, Scheel E. Quality of freeze-dried (lyophilized) quarantined single-donor plasma. *Transfusion* 2013;**53**(12):3203–9.

23. Garrigue D, Godier A, Glacet A, Labreuche J, Kipnis E, Paris C, *et al.* French lyophilized plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial. *J Thromb Haemost* 2018;**16**(3):481–9.

24. Guyette FX, Sperry JL, Peitzman AB, Billiar TR, Daley BJ, Miller RS, *et al.* Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the prehospital air medical plasma trial. *Ann Surg* 2021;**273**(2):358–64.

25. Shackelford SA, del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, *et al.* Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA: J Am Med Assoc* 2017;**318**(16):1581–91.

26. O'Reilly DJ, Morrison JJ, Jansen JO, Apodaca AN, Rasmussen TE, Midwinter MJ. Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study. *J Trauma Acute Care Surg* 2014;**77**(3 Suppl. 2):S114–20.

27. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Critical Care* 2019;**23**(1):98.

28. Foukaneli D, Bassey S, Bend M. Survey of group O D negative red cell use: NHS Blood and Transplant. 2018. URL: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17159/o-neg-survey-2018-final2.pdf (accessed 21 December 2021).

29. NHS Blood and Transplant. *NHSBT Hospital Blood Supply Chain 2017/18 Annual Report*. London: NHS Blood and Transplant; 2018.

30. McCullagh J, Proudlove N, Tucker H, Davies J. Making every drop count: reducing wastage of a novel blood component for transfusion of trauma patients. *BMJ Open Qual* 2021;**10**:1396.

31. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, *et al.*; PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018;**379**(8):711–21.

32. US Department of Health and Human Services Food and Drug Administration. *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards*. URL: www.fda.gov/media/136238/download (accessed 21 December 2021).
33. Orkin AM, Gill PJ, Ghersi D, Campbell L, Sugarman J, Emsley R, *et al.*; CONSERVE Group. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA* 2021;**326**(3):257–65.
34. Reynolds PS, Michael MJ, Cochran ED, Wegelin JA, Spiess BD. Prehospital use of plasma in traumatic hemorrhage (The PUPTH Trial): study protocol for a randomised controlled trial. *Trials* 2015;**16**:321.
35. London's Air Ambulance Charity. *UK'S First Air Ambulance to Carry Blood on Board*. 2013. URL: www.londonsairambulance.org.uk/news-and-stories/charity/uks-first-air-ambulance-to-carry-blood-on-board (accessed 25 February 2022).
36. O'Neill J, Jarman H, Greenhalgh R, Russell M, Lyon R. *Pre-hospital Blood Transfusions on a UK Air Ambulance Service: The First Ten Months*. Kent: Kent, Surrey and Sussex Helicopter Emergency Medical Service; 2014.
37. Thies KC, Truhlář A, Keene D, Hinkelbein J, Rützler K, Brazzi L, Vivien B. Pre-hospital blood transfusion: an ESA survey of European practice. *Scand J Trauma Resusc Emerg Med* 2020;**28**(1):79.
38. Griggs JE, Jeyanathan J, Joy M, Russell MQ, Durge N, Bootland D, *et al.*; Kent, Surrey and Sussex Air Ambulance Trust. Mortality of civilian patients with suspected traumatic haemorrhage receiving pre-hospital transfusion of packed red blood cells compared to pre-hospital crystalloid. *Scand J Trauma Resusc Emerg Med* 2018;**26**(1):100.
39. Rehn M, Weaver AE, Eshelby S, Røislien J, Lockey DJ. Pre-hospital transfusion of red blood cells in civilian trauma patients. *Transfus Med* 2018;**28**(4):277–83.
40. Tucker H, Avery P, Brohi K, Davenport R, Griggs J, Weaver A, Green L. Outcome measures used in clinical research evaluating prehospital blood component transfusion in traumatically injured bleeding patients: a systematic review. *J Trauma Acute Care Surg* 2021;**91**(6):1018–24.
41. Yazer MH, Cap AP, Glassberg E, Green L, Holcomb JP, Khan MA, *et al.* Toward a more complete understanding of who will benefit from prehospital transfusion. *Transfusion* 2022;**62**:1671–9.
42. Crombie N, Doughty HA, Bishop JRB, Desai A, Dixon EF, Hancox JM, *et al.* Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Haematol* 2022;**9**:250–61.
43. Chapman MP, Moore EE, Chin TL, Ghasabyan A, Chandler J, Stringham J, *et al.* Initial experience with a randomized clinical trial of plasma-based resuscitation in the field for traumatic hemorrhagic shock. *Shock* 2015;**44**:63–70.
44. *Prehospital Transfusion Strategy in Bleeding Patients*. 2021. URL: www.clinicaltrials.gov/ct2/show/NCT04879485 (accessed 28 September 2022).
45. Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, *et al.* A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Ann Surg* 2013;**258**:527–33.
46. *Type O Whole Blood and Assessment of Age During Prehospital Resuscitation Trial*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT04684719 (accessed 28 September 2022).

47. *Study of Whole Blood In Frontline Trauma*. URL: www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/swift/ (accessed 21 December 2021).

48. Woolley T, Thomson P, Kirkman E, Reed R, Ausset S, Beckett A, *et al.* Trauma Hemostasis and Oxygenation Research Network position paper on the role of hypotensive resuscitation as part of remote damage control resuscitation. *J Trauma Acute Care Surg* 2018;**84**:S3–13.

49. Shakur H, Roberts I, Afolabi A, Brohi K, Coats T, Dewan Y, *et al.*; CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;**377**:1096–101.

50. Haywood K, Whitehead L, Nadkarni VM, Felix A, Beesems S, Böttiger BW, *et al.* COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Resuscitation* 2018;**127**:147–63.

Appendix 1 The RePHILL Collaborative Group

Trial Management Group

Prof. Gavin Perkins, Dr Nicholas Crombie, Iain Smith, Dr Heidi Doughty, Dr David Naumann, Hazel Smith, Dr Margaret Grant, Gemma Slinn, Dr Rebekah Wale, Emily Dixon, Dr Karen Piper, Deborah Papoola, Amisha Desai, Natalie Ives, Dr Jon Bishop

Data Monitoring Committee

Prof. John Nicholl (Chair), Dr Jan Jansen, Prof. Fiona Lecky

Trial Steering Committee

Prof. Ian Roberts (Chair), Prof. John Holcomb, Dr Simon Stanworth, Prof. Jason Smith, Prof. Timothy Coats, Andrew Cox, Timothy Marshall

Blood Banks and Pharmacies

Mike Herbert, Mindy Sahota (New Cross Hospital); Camran Khan, Zeeshan Parvez (Worcester Acute Hospital); Tina Taylor, Julie Nortcote, Mojid Khan (University Hospitals Coventry and Warwickshire); Claire Newsam, Katherine Philpott, Lynne Whitehead (Addenbrooke's Hospital); Debbie Asher, Gail Healey (Norfolk and Norwich University Hospital)

Blood Bikers

Midland Freewheelers, Warwickshire and Solihull Blood Bikers

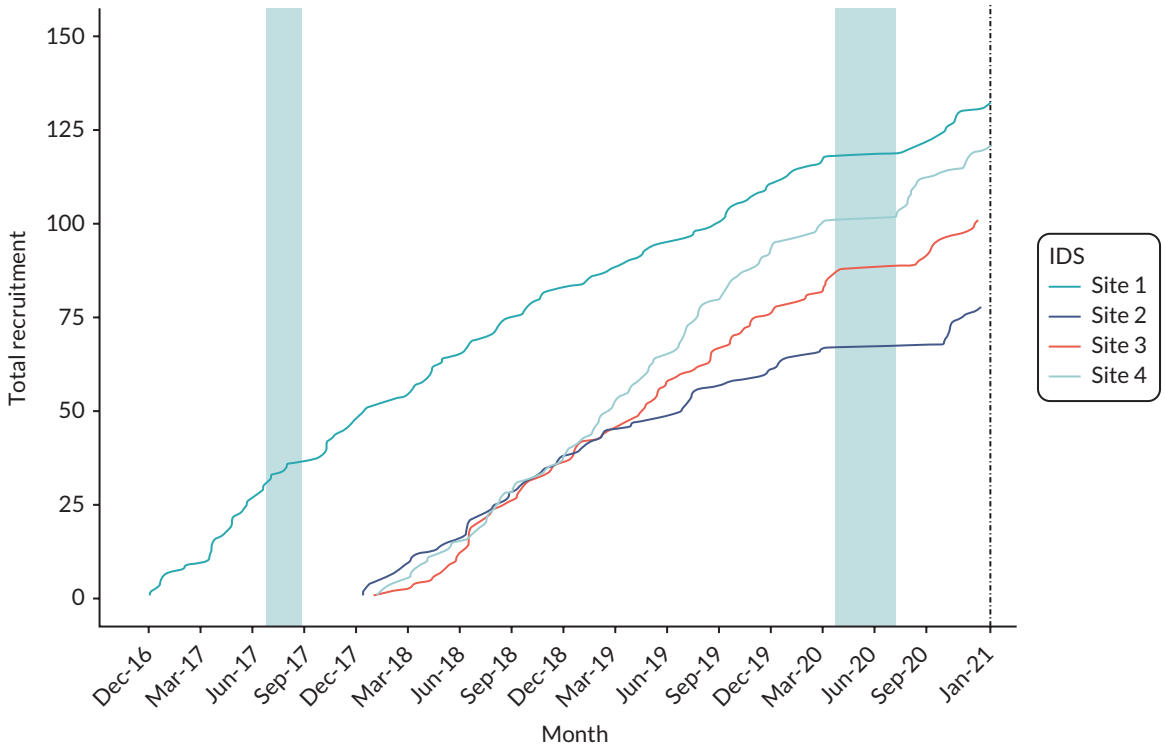
Air Ambulance Sites (IDS)

Alistair Wilson (PI), Pam Chrispin (PI), Richard Hinson (East Anglian Air Ambulance); Caroline Leech (PI), Mark Beasley, Sam Cooper (The Air Ambulance Service); Mark Nash (PI) (West Midlands Ambulance Service); Simon Lewis (PI), Oliver Robinson, Rod Mackenzie (Magpas Air Ambulance)

Receiving Hospital Sites

David Yeo (PI; Queen Elizabeth Hospital); Caroline Leech (PI; University Hospitals Coventry and Warwickshire); Tom James (University Hospitals of North Midlands); Jason Kendall (PI), Johannes von Vopelius-Feldt (PI) (Southmead Hospital Bristol); Christopher Gough (PI) (Queen's Medical Centre Nottingham); Gary Mills (PI; Northern General Hospital Sheffield); Aquib Hafeez (PI; Oxford University Hospitals); Sarah Hazleman (PI; Addenbrooke's Hospital); Francoise Sheppard (PI; Norfolk and Norwich University Hospital); Ben Bloom (PI; Royal London Hospital)

Appendix 2 Recruitment by site



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