

RePHILL

Smith, Iain M; Crombie, Nicholas; Bishop, Jonathan R B; McLaughlin, Aisling; Naumann, David; Hancox, James; Slinn, Gemma; Ives, Natalie; Grant, Margaret; Perkins, Gavin D; Doughty, Heidi; Midwinter, Mark

DOI:

[10.1111/tme.12486](https://doi.org/10.1111/tme.12486)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Smith, IM, Crombie, N, Bishop, JRB, McLaughlin, A, Naumann, D, Hancox, J, Slinn, G, Ives, N, Grant, M, Perkins, GD, Doughty, H & Midwinter, M 2018, 'RePHILL: Protocol for a randomised controlled trial of pre-hospital blood product resuscitation for trauma', *Transfusion Medicine*, vol. 28, no. 5, pp. 346-356. <https://doi.org/10.1111/tme.12486>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is the peer reviewed version of the following article Smith, I. M., Crombie, N., Bishop, J. R., McLaughlin, A., Naumann, D. N., Herbert, M., Hancox, J. M., Slinn, G., Ives, N., Grant, M., Perkins, G. D., Doughty, H., Midwinter, M. J. and on behalf of the RePHILL Trial Collaborators (2017), RePHILL: protocol for a randomised controlled trial of pre-hospital blood product resuscitation for trauma. *Transfusion Med*, which has been published in final form at 10.1111/tme.12486. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

**RePHILL: Protocol for a randomised controlled trial
of pre-hospital blood product resuscitation for trauma**

Iain M Smith¹, Nicholas Crombie^{1,2,3,4}, Jonathan R Bishop^{1,5}, Aisling McLaughlin¹,
David N Naumann¹, Mike Herbert⁶, James M Hancox^{1,4}, Gemma Slinn⁵,
Natalie Ives⁵, Margaret Grant⁵, Gavin D Perkins^{3,7,8}, Heidi Doughty⁹
and Mark J Midwinter^{1,10}, on behalf of the RePHILL Trial Collaborators

¹NIHR Surgical Reconstruction & Microbiology Research Centre, University of Birmingham, Birmingham, UK

²Department of Anaesthesia, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

³West Midlands Ambulance Service Medical Emergency Response Incident Team, Brierley Hill, UK

⁴Midlands Air Ambulance, Stourbridge, UK

⁵Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK

⁶Department of Haematology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK

⁷Warwick Clinical Trials Unit, University of Warwick, Coventry, UK

⁸Critical Care Unit, Heart of England NHS Foundation Trust, Birmingham, UK

⁹NHS Blood and Transplant, Birmingham, UK

¹⁰School of Biomedical Sciences, University of Queensland, Australia

Corresponding Author:

Dr Nicholas Crombie FRCA

Co-Chief Investigator, RePHILL

NIHR Surgical Reconstruction & Microbiology Research Centre

4th Floor, North Block

Institute for Translational Medicine

Heritage Building

Queen Elizabeth Hospital

Birmingham, B15 2TH, United Kingdom

Email: nicholas.crombie@uhb.nhs.uk

Phone: +44 (0) 780 123 1589

Running Title: Pre-hospital blood products for trauma – RCT protocol

Keywords: Wounds and Injuries

Haemorrhage

Emergency Medical Services

Blood Transfusion

Randomised Controlled Trial

Word count: 4993

ABSTRACT

Objectives

To describe the “Resuscitation with Pre-Hospital blood products” trial (RePHILL) - a multi-centre randomised controlled trial of pre-hospital blood product (PHBP) administration versus standard care for traumatic haemorrhage.

Background

PHBP are increasingly used for pre-hospital trauma resuscitation despite a lack of robust evidence demonstrating superiority over crystalloids. Provision of PHBP carries additional logistical and regulatory implications, and requires a sustainable supply of universal blood components.

Methods

RePHILL is a multi-centre, two-arm, parallel group, open-label, phase III randomised controlled trial currently underway in the UK. Patients attended by a pre-hospital emergency medical team, with traumatic injury and hypotension (systolic blood pressure < 90 mmHg or absent radial pulse) believed to be due to traumatic haemorrhage are eligible. Exclusion criteria include: age < 16 years, blood product receipt on scene prior to randomisation, Advanced Medical Directive forbidding blood product administration, pregnancy, isolated head injury and prisoners. 490 patients will be recruited in a 1:1 ratio to receive either the intervention (up to two units of red blood cells and two units of lyophilised plasma) or the control (up to 4 boluses of 250 ml 0.9% saline). The primary outcome measure is a composite of failure to achieve lactate clearance of $\geq 20\%$ per hour over the first two hours after

randomisation and all-cause mortality between recruitment and discharge from the primary receiving facility to non-acute care. Secondary outcomes include pre-hospital time, coagulation indices, in-hospital transfusion requirements and morbidity.

Conclusions

RePHILL will provide high quality evidence regarding the efficacy and safety of PHBP resuscitation for trauma.

INTRODUCTION

The last two decades have seen great changes in trauma resuscitation practice (Holcomb, 2017). Hospital treatment of haemorrhagic shock increasingly emphasises early use of blood products and minimisation of crystalloids – previously the mainstay of pre-hospital and in-hospital volume replacement. Major haemorrhage protocols have been widely adopted to deliver plasma in high ratios to red blood cells (RBC) early in resuscitation. Improved survival from such strategies has been reported in both military and civilian settings (Bhangu *et al.*, 2013; Murad *et al.*, 2010). Delivery may nonetheless require significant performance improvement; data published in 2016 showed that only 2% of UK trauma haemorrhage patients received “optimum” plasma:RBC ratios ($\geq 1:2$), with average delay to first plasma transfusion exceeding one hour (Stanworth *et al.*, 2016).

Pre-hospital blood product (PHBP) administration is a key element of “Remote Damage Control Resuscitation” (Jenkins *et al.*, 2014a). It reduces time-to-transfusion and may improve survival. Various PHBP combinations have been deployed by pre-hospital emergency medical (PHEM) providers (Dalton, 1993; Glassberg *et al.*, 2013; O'Reilly *et al.*, 2014a; Sunde *et al.*, 2015; Wales Air Ambulance, 2015; Weaver *et al.*, 2013; Zielinski *et al.*, 2017). Although a biological case for the superiority of PHBP resuscitation can be made (Holcomb *et al.*, 2015a), our group’s systematic review of the clinical literature reported that the majority of evidence was of “very low quality” (as defined by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (Kerwin *et al.*, 2012)) from which no reliable conclusions could be drawn (Smith *et al.*, 2016). Recently released UK national

guidelines for trauma management (National Institute for Health and Clinical Excellence, 2016) did not examine any pre-hospital transfusion studies. **Instead, pre-hospital guidance was extrapolated from one in-hospital cohort study of patients receiving 10u RBC in the first 24h after admission (Neal *et al.*, 2012).**

“A Multi-Centre Randomised Controlled Trial of Pre-Hospital Blood Product Administration versus Standard Care for Traumatic Haemorrhage” (abbreviated title: “Resuscitation with Pre-Hospital blood products” or “RePHILL”) is a randomised controlled trial (RCT) which will investigate the hypothesis that pre-hospital administration of up to two units each of RBC and lyophilised (freeze-dried) plasma (LP) will improve tissue perfusion (as measured by lactate clearance) and reduce mortality in trauma patients with haemorrhagic shock compared to the current practice of the majority of UK PHEM services of crystalloid resuscitation.

MATERIALS AND METHODS

Trial Design

This study is a multi-centre, two-arm, parallel group, open-label, interventional phase III RCT of 490 patients. An internal pilot phase was included to validate trial logistics. The trial schema is shown in figure 1. This protocol conforms to the SPIRIT guidelines (Chan *et al.*, 2013). The pilot phase began recruitment in December 2016, with approval to continue into the main trial received in June 2017. **Recruitment is expected to continue until 2020.**

Trial Objectives

Primary Objective

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

Secondary Objectives

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

- a. improves blood pressure, heart rate and capillary oxygenation on arrival to the Emergency Department (ED).
- b. does not prolong pre-hospital time.
- c. reduces pre-hospital fluid requirements.
- d. reduces in-hospital transfusion requirements.
- e. reduces trauma-induced coagulopathy.
- f. preserves platelet function.

- g. does not lead to a greater incidence of transfusion-related complications, particularly acute respiratory distress syndrome (ARDs).
- h. does not lead to **significant** blood product wastage.

Outcomes

Primary Outcome

The primary outcome is a composite measure consisting of episode mortality (death from all causes between trial entry and discharge from the primary receiving facility to non-acute care) and failure to achieve lactate clearance of $\geq 20\%$ /hr over the first two hours after randomisation. **Regnier *et al* (2012) studied this endpoint, reporting that mortality amongst such patients is approximately 20%, similar to the 23% mortality in trauma patients with a comparable degree of hypotension to those eligible for RePHILL (Hasler *et al.*, 2011, 2012). Lactate clearance is thus a clinically meaningful biochemical predictor of outcome, but subject to minimal confounding from in-hospital interventions.** Table 1 describes calculation of lactate clearance.

Secondary Outcomes

Secondary outcomes are listed in Table 2.

Sample Size Calculation

Although no definitive data exists on this composite outcome, observational studies suggest potentially dramatic reductions in mortality from civilian pre-hospital RBC (Brown *et al.*, 2015b) and military pre-hospital RBC combined with thawed plasma (O'Reilly *et al.*, 2014b). Following consultation with experts in pre-hospital trauma resuscitation, it is considered that an absolute reduction of 10% in the

proportion of patients experiencing one of the component primary outcomes is clinically meaningful and is an appropriate effect size upon which to base the power calculation.

To detect an absolute difference of 10% between groups in the proportion of patients experiencing either component of the primary outcome (i.e. from 20% in the standard care group to 10% in the group receiving PHBP) using the method of difference between proportions (2-sided Fisher's Exact Test) with 80% power, and a type 1 error rate of 5% (i.e. $\alpha=0.05$), requires 438 participants. Allowing and adjusting for a 10% loss to follow-up, 490 participants are required.

Setting

The study takes place in three regional major trauma networks in England (West Midlands, East Midlands, East of England). These networks consist of integrated National Health Service (NHS) ambulance services and PHEM teams, supported by six charity-funded air ambulances, and NHS hospitals designated as Major Trauma Centres and Trauma Units. PHEM teams consist of a Critical Care Paramedic and a doctor at a minimum level of a specialty registrar sub-specialising in PHEM. Patients will be identified and entered into the trial by the relevant PHEM doctors.

Eligibility criteria

Entry criteria for RePHILL participants are listed in Table 3.

Trial Interventions

All trial-specific processes were designed to minimise any prolongation of pre-hospital time.

Experimental Intervention

The trial intervention is up to two units of RBCs (blood group O RhD negative, Kell negative) and two units of LyoPlas N-w, blood groups A or AB (DRK-Blutspendedienst West, Ratingen, Germany) (see Source of LP), delivered as single-unit boluses in the following sequence: one unit RBC, one unit LyoPlas N-w, one unit RBC, one unit LyoPlas N-w). This sequence was chosen as the most efficient, allowing the first unit of RBC to be delivered while LyoPlas N-w is being reconstituted. Both LyoPlas N-w units in single intervention are the same blood group.

Control Intervention

The control intervention is up to four 250ml boluses of 0.9% saline. This was chosen because it is the most common crystalloid used by the PHEM services in the UK for trauma resuscitation (D. Naumann *et al*, unpublished data). This allows comparison of PHBP against existing standard care.

The average volume of one unit of RBC is approximately 270 ml (range: 220-340), while reconstituted Lyoplas N-w is 213ml. Thus one unit each of RBC and LP have a comparable volume to two saline boluses.

Delivery of interventions

Participants receive up to four boluses of the assigned intervention to restore and maintain SBP \geq 90mmHg or a palpable radial pulse. **This is assessed after each bolus. If SBP is restored before all intervention boluses are administered, but subsequently falls, interventions continue from the point at which delivery was paused.** All interventions should be administered through fluid warmers and may be administered by intravenous or intraosseous route. **If additional fluid is required to maintain blood pressure, further 250ml boluses of 0.9% saline may be given according to normal local practice.** All other pre-hospital and in-hospital care proceeds as directed by the treating clinicians.

Practical considerations leading to the choice of 1:1 blood product ratio

Various factors lead to the selection of a combination of RBC and LP as the trial intervention. Optimum blood product ratios remain a matter of debate. The Prospective Observational Multicentre Major Trauma Transfusion cohort study found that failure to achieve plasma or platelet:RBC ratios of at least 1:2 during the first six hours from admission was associated with significantly higher mortality than amongst patients who received at least 1:1 (Holcomb *et al.*, 2013). In contrast, the Pragmatic Randomized Optimal Platelet and Plasma Ratios RCT found no difference in overall mortality between plasma, platelets and RBCs administered in a ratio of 1:1:1 donor units compared to 1:1:2 (Holcomb *et al.*, 2015b). In observational studies, hospital-based administration of plasma within the first six units of blood products is associated with a 66% reduction in the odds ratio for 30-day mortality (del Junco *et al.*, 2013). Pre-hospital administration of 1:1 ratios of thawed plasma and RBC to battlefield casualties has been associated with a 58% reduction

in mortality compared to historical injury-matched controls (O'Reilly *et al.*, 2014b). Plasma:RBC ratios of 1:1 are perceived as offering the maximum possible benefit. RePHILL seeks to deliver this from as close to the time of injury as possible.

Rationale for Lyophilised plasma rather than fresh frozen plasma

Various approaches to the delivery of plasma in the field have been described. Fresh frozen plasma (FFP) can be carried by ground ambulance for rapid on-site thawing (Moore *et al.*, 2015), but requires custom-made packaging and significant investment in equipment for each ambulance installation. Pre-thawed plasma is suitable for situations where the PHEM team deploy from a base close to the blood bank and where unused product can be rotated back into stock with an expectation use before expiry to avoid wastage. This logistic model was used by the UK Defence Medical Services in Afghanistan, based around a five-day post-thaw shelf-life (O'Reilly *et al.*, 2014a). A similar approach in a US civilian study reported less than 2% wastage of blood products (Holcomb *et al.*, 2015a). UK regulations at the time of trial design limited the post-thaw shelf-life of FFP to 24 hours (this post-thaw period was extended to 5 days in 2016). UK civilian PHEM teams typically deploy by helicopters based at airfields remote from medical facilities. Given the relative infrequency of exsanguinating trauma in the UK, reliance on pre-thawed plasma might be unacceptably wasteful. In contrast, LP can be stored at room temperature for up to 15 months and reconstituted for use in as little as five minutes. Its suitability for the pre-hospital environment is demonstrated by the Israeli military's decision to replace pre-hospital crystalloid with LP as the resuscitation fluid of choice (Glassberg *et al.*, 2013). The French military utilise a French-produced LP as its sole plasma product on operations (Sailliol *et al.*, 2013), while the UK Defence Medical Services

introduced LyoPlas N-w for remote operations in 2012 (Gokhale *et al.*, 2016). Norwegian civilian helicopter emergency medical services have carried LP since 2013 (Zielinski *et al.*, 2017).

Source of blood products

LyoPlas N-w is a lyophilised plasma manufactured by the German Red Cross. Individual units are manufactured from single donations. It is licensed in Germany (license PEI.H.03075.01.1) for the same indications as FFP. Approval for the import and use of LyoPlas N-w as an Investigational Medical Product for the purposes of this trial was granted by the UK Medicines and Healthcare Regulatory Authority (MHRA) (Clinical Trials Authorisation: 16719/0228/001-0001).

The RBC used in RePHILL are blood group O, RhD negative, Kell negative, leucodepleted RBC in saline, adenine, glucose and mannitol (SAG-M) additive solution, drawn from national NHS Blood and Transplant stocks supplied by the blood banks that are supporting the trial. A summary of standard collection and processing is included as supplementary material.

Regulatory Framework

The MHRA considers LyoPlas N-w to be a pharmaceutical, rather than a blood product in view of the post-donation processing (Joint UKBTS/NIBSC Professional Advisory Committee, 2010). RePHILL is conducted in accordance with the amended Clinical Trials Regulations (2004, 2006), Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of

Pharmaceuticals for Human Use, 1996) and the Declaration of Helsinki (World Medical Association, 2013).

Randomisation

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

Nominated personnel at each blood bank obtain randomised allocations via a secure online randomisation system (accessible 24 hours per day). Blood banks are supplied with pre-printed “treatment box number” labels. The allocated trial intervention is then packed in transport boxes, secured with tamper-proof seals and labelled with the specified box numbers.

Pre-recruitment blinding

Each intervention is issued in two sealed, thermally stable transport boxes (conditioned for the different storage requirements of RBC and LP), **labelled with the same “treatment box number” as issued by the Trial Coordinating Centre**. For crystalloid interventions, each box contains two 250ml 0.9% saline. For PHBP interventions, one container contains two units of RBCs, the other contains two units of LyoPlas N-w. Additional weight is added to boxes containing crystalloid to ensure that the intervention cannot be predicted by box weight. Sealed and numbered transport boxes are delivered to PHEM services by courier. These remain sealed

until after a decision has been made to enter a patient into the trial. **Only one intervention is carried at a time. This removes any need for the PHEM team to contact the Trial Coordinating Centre during the pre-hospital phase which would both delay treatment and risk loss to recruitment if communications could not be established.**

To ensure that pre-recruitment blinding is maintained, the integrity of seals is subject to 100% audit on the return of unused interventions. This also confirms that interventions have been kept in the appropriate conditions and that no tampering has taken place.

Patient Randomisation, Enrolment and Lactate Measurement

The PHEM doctor assesses the potential participant's vital signs on scene and confirms if eligible for entry into the RePHILL trial. If they fulfil the eligibility criteria, a capillary blood lactate concentration is measured and the treatment boxes opened. The randomised study intervention is revealed and given to the patient. Participants are considered entered into the trial when the PHEM team open the first treatment box.

Eligibility is documented at the Receiving Hospital Site, and the participant is enrolled into the trial and assigned a Trial Number. Participants who are later found to be ineligible, but who have received the trial interventions will remain in the trial as per protocol and included in the analysis, if they consent to this.

Venous lactate concentration is measured on arrival at ED as part of a standard trauma admission blood draw. A further venous lactate will be drawn two hours after arrival at the ED as part of RePHILL.

Consent

Legal framework for research in patients lacking capacity

As the occurrence of major trauma is unpredictable and immediately incapacitating, prospective informed consent from participants is not possible. In the rare event that a participant retains capacity at trial entry, their clinical condition will require immediate resuscitation. It would be inappropriate to delay life-saving treatment and transport in order to seek informed consent. UK legislation permits emergency care research to begin in such contexts (Clinical Trials Regulations 2004 (as amended); Human Tissue Act 2004 (as amended)) **and has been applied in the PARAMEDIC-2 RCT of adrenaline in out-of-hospital cardiac arrest** (Perkins *et al.*, 2015, p17).

Details of the relevant legislation are provided as supplementary material.

Consent in RePHILL

Consent to continue in RePHILL is sought at the earliest appropriate opportunity. **In practical terms, this consent is to continue data collection as most trial processes will have occurred prior to any opportunity to seek informed consent from a participant or appropriate representative.** Initial consent is usually sought from a professional legal representative shortly after arrival at the receiving hospital, as it is rare for either the participant to retain capacity at this time, or for a personal legal representative to be available. As with PARAMEDIC-2, this is deemed to be at a point when the participant is no longer critically ill. An approach to patient or personal legal

representative can then be made at a time when they are better able to retain and consider information.

The most challenging ethical consideration in this trial relates participants who die prior to consent being obtained. RePHILL employs a passive information approach, consistent with previous and ongoing emergency care studies (Perkins *et al.*, 2015), placing information in locations likely to be visited by relatives of the deceased. The information contains a brief summary of the trial and contact details for those wishing further information. Further details of the rationale for this approach is provided as supplementary material.

Jehovah's Witnesses

Jehovah's Witnesses hold beliefs which prohibit the receipt of blood transfusions.

Normal trauma resuscitation practice in EDs and amongst PHEM teams currently delivering PHBP is to search for an Advance Medical Directive (AMD), identifying a patient as a Jehovah's Witness prior to the administration of blood products.

Clinicians involved in RePHILL perform the same rigorous checks in the pre-hospital environment, prior to recruitment. Liaison with representatives of the Hospital Liaison Committees for Jehovah's Witnesses and national Jehovah's Witnesses Hospital Information Services took place during trial design and implementation to ensure that information regarding RePHILL was communicated to potentially affected communities.

Additional Trial Procedures and Assessments

The standard admission blood draw on ED arrival includes full blood count, prothrombin time and International Normalised Ratio. Transfusion measures include blood grouping and assessment of mixed-field blood groups. Selected sites will also assess coagulation by viscoelastic methods (ROTEM™) and platelet function (MultiPlate™). Other assessments are summarised in Table 2. Data collection ends at the earliest of discharge from the acute care facility, death or 30 days, unless consent is withdrawn earlier. Mortality data will continue to be collected for participants who remain in an acute care facility beyond 30 days.

Safety Considerations

The additional risk to participants in RePHILL is considered to be minimal. As discussed above, “standard care” recipients receive treatment identical to that which they would receive outwith the trial whereas PHBP recipients receive treatment equivalent to that which they would receive on arrival at an ED.

Transfusion safety

The plasma from which LyoPlas N-w is produced is filtered, rendering it “virtually cell-free”. LyoPlas N-w is only produced from leucocyte-antibody negative plasma, minimising risk of transfusion-related acute lung injury (DRK-Blutspendedienst West, 2017). LP transfusion is safe, with no reported transfusion reactions associated with French LP (Martinaud *et al.*, 2011) or the previous German mini-pool LP (Schoenfeld *et al.*, 2010), while the incidence of transfusion reactions associated with LyoPlas N-w is no different from that of FFP (Bux *et al.*, 2013; DRK-Blutspendedienst West, 2017). Systematic review of PHBP resuscitation for trauma identified only two

potential pre-hospital transfusion reactions, both associated with RBC transfusion, amongst 759 PHBP recipients (Smith *et al.*, 2016). A third potential event (associated with LyoPlas N-w) was reported subsequently (Shlaifer *et al.*, 2017) in a cohort of 109 recipients. A true transfusion reaction was considered the most likely explanation in only of these (associated with pre-hospital RBC transfusion). In contrast, UK haemovigilance monitoring reports the rate of allergic, hypotensive or severe febrile reactions to FFP as one per 721 units issued (Bolton-Maggs *et al.*, 2016).

LyoPlas N-w is produced by a quarantined single donor process – plasma is only processed if a donor retests negative for blood-borne pathogens at least four months after the donation was received, thus minimising the risk of blood borne virus transmission (Bux *et al.*, 2013). Based on previous national modelling (Advisory Committee on the Safety of Blood, 2013), transmission of prion disease (particularly variant Creutzfeld-Jakob Disease) is not considered a hazard of this study (for full discussion, see supplementary material).

Transfer delay

Delivering PHBP has the potential to incur a delay in transfer to definitive haemorrhage control, increasing risk to patients. This is reported as a secondary outcome and is one of the safety considerations to be monitored by the DMEC.

Adverse Event Reporting

Adverse events will be reported in accordance with statute (Clinical Trials Regulations 2004), using standard definitions of events and causality. Given the high

mortality and morbidity anticipated in a major trauma population, certain Serious Adverse Events (SAEs) are exempt from expedited reporting (Table 4). SAEs relating to a pre-existing condition will not be reported.

The inclusion of RBC as a component of the intervention mandates compliance with normal haemovigilance requirements. Transfusion-related adverse events are to be reported to both the coordinating blood bank for the relevant IDS and via the Serious Hazards Of Transfusion and Serious Adverse Blood Reactions and Events (SHOT/SABRE) in accordance with the EU Blood Safety Directive (2005).

Internal Pilot Phase

RePHILL successfully completed an internal pilot phase to assess trial logistics, validate the multi-centre aspects of the trial and confirm that it was both feasible and practical to continue to recruit into the main trial. At the end of the pilot phase, the following targets were set to justify progression to the main trial:

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

Statistical Methods

The primary comparison will be those randomised to resuscitation with PHBP versus those randomised to resuscitation with 0.9% saline (standard care). All primary analyses will be based on the intention-to-treat principle. For all major outcome measures, summary statistics and differences between groups (e.g. mean differences, relative risks, hazard ratios) will be presented with 95% confidence intervals (CIs) and p-values from 2-sided tests also given. Outcomes will be adjusted for the stratification variable, IDS, where possible. A p -value <0.05 will be considered statistically significant. No adjustment for multiple comparisons will be made.

Primary outcome analysis

The primary outcome is a binary composite measure of episode mortality and early lactate clearance. A relative risk and 95% CI will be calculated using log-binomial regression modelling. Individual components will also be reported in accordance with the recommendations of Ferreira-Gonzalez *et al.* (2007).

Secondary outcome analysis

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

Subgroup analyses

Eleven *a priori* subgroup analyses are planned with respect to the primary outcome measure (Table 5). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimates within subgroups. The results of subgroups will be treated with caution and will be used for the purposes of hypothesis generation only.

Missing data and Sensitivity Analyses

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

Data Monitoring and Ethics Committee (DMEC)

An independent DMEC has been established to oversee the safety of participants in the trial. The DMEC met prior to the trial opening to enrolment and after the internal pilot phase to assess the safety data and advised on continuation to the main phase III trial. The DMEC will now meet at least annually. Interim analyses of major outcome measures and safety data will be conducted and provided in strict

confidence to the DMEC, which will consider whether the accumulated data from the trial, together with the results from other relevant research, justifies continued recruitment of further participants. The DMEC operates in accordance with a trial specific charter.

Dissemination

The trial results will be reported in accordance with the CONSORT guidelines (Schulz *et al.*, 2011) and will be submitted for publication in peer-reviewed journals and presentation at appropriate national and international academic meetings. Trial participants will be sent a summary of the final results, including references to full papers. RePHILL data may be made available to external groups wishing to undertake original analysis, subject to approval from the Trial Management Group.

DISCUSSION

Early blood product transfusion and reduced crystalloid administration has been associated with improved survival in observational, predominantly retrospective, military and civilian studies (Bhangu *et al.*, 2013; Murad *et al.*, 2010; Rajasekhar *et al.*, 2011). Projection of blood products into the pre-hospital phase of trauma care is intuitively attractive; however the use of PHBP is both logistically challenging and resource intensive, and is not without risk (Bolton-Maggs, 2015). The most significant and immediate risk of ABO incompatibility may be managed by use of “universal components”. This, however, has implications for resource management. Although “universal” plasma donors (group AB) constitute only 4% of the UK donor pool (NHS Blood and Transplant, 2014), low anti-B titre group A pre-thawed FFP is

more available and is an established source of emergency plasma transfusions in patients of unknown ABO group in North American Trauma Centres (Dunbar *et al.*, 2016). The success and safety of this approach has been reflected in recently published UK guidelines (Hunt *et al.*, 2015). However, this represents a logistical challenge for helicopter-based services which frequently deploy from airfields remote from the blood banks that support them. Alternative forms of plasma with longer shelf-lives need to be considered, such as the LP used in RePHILL. In addition, provision of an adequate supply of “universal” group O RhD negative red cell concentrates (drawn from only 8% of the UK donor pool) remains challenging. Group O RhD negative, Kell negative red cell concentrates should ideally be reserved for female recipients of child bearing age (Hunt *et al.*, 2015). Such resource management is impractical in the pre-hospital environment due to the constraints on space and weight inherent in helicopter-based service. **Hypothetically, early “haemostatic” resuscitation might reduce overall transfusion requirements, thus preserving blood products stocks. However, no such benefit has been demonstrated to date (Smith *et al.*, 2016).**

A convincing case for PHBP that justifies utilisation of scarce universal donor resources cannot be made from the published literature, with only “low” and “very low” quality evidence, derived from entirely observational studies (predominantly retrospective case series) (Smith *et al.*, 2016). More recent retrospective military data found an association between a directive mandating pre-hospital helicopter evacuation of critically injured battlefield casualties within 60 minutes of wounding and a reduction in mortality (Kotwal *et al.*, 2016). One component of this may have been the delivery of PHBP. However, in common with the majority of studies in this

field, missing data and potential confounding was such that the “influence on morbidity and mortality could not be reliably measured”.

Experts in the field have called for “prospective studies...to clarify the role of [freeze-dried plasmas] and RBCs in civilian prehospital hemorrhagic shock resuscitation” (Sunde *et al.*, 2015) and have stressed the importance of “high-quality prospective...data collection” (Jenkins *et al.*, 2014b). A prospective observational study recently reported no evidence of superiority of PHBP in reducing mortality, but was limited by significant differences in trauma burden and physiology between patients retrieved by PHBP-capable services compared to those transported without access to PHBP (Holcomb *et al.*, 2017). The authors concluded that “large, multicentre randomized studies [are] required”.

Five PHBP RCTs have attempted to meet this need. Two have terminated early (Shackelford, 2017) due to futility (Control Of Major Bleeding After Trauma - COMBAT) (Moore *et al.*, 2015) or insufficient recruitment (Pre-Hospital Use of Plasma for Traumatic Hemorrhage - PUPTH) (Reynolds *et al.*, 2015). Other than RePHILL, ongoing studies include the Prehospital Air Medical Plasma study (PAMPer) (Brown *et al.*, 2015a) and the Pre-hospital Administration of Lyophilized Plasma for Post-traumatic Coagulopathy Treatment (PREHO-PLYO) (Jost and Lanoe, 2017). PAMPer compares two units of thawed plasma against standard care in a US trauma population and aims to recruit 530 patients. PREHO-PLYO is a smaller French study of 140 patients investigating the effect of lyophilised plasma on coagulation. The study size calculations for RePHILL and PAMPer are broadly similar. However, PAMPer seeks to detect a 67% relative reduction from a baseline

of 22% 30-day mortality, whereas RePHILL's inclusion of a measure of resuscitation efficacy in the composite primary outcome allows assessment of a more modest treatment effect with greater focus on that part of the patient's trauma journey most likely to be affected by pre-hospital intervention. In addition, mechanisms of injury differ between the USA and UK; PAMPer is likely to recruit a higher proportion of penetrating trauma victims whereas a preponderance of blunt trauma is anticipated amongst RePHILL participants. Thus PAMPer and RePHILL are complementary studies that have the potential to increase knowledge of the response to trauma resuscitation across a spectrum of injury.

CONCLUSIONS

RePHILL provides a timely and unique opportunity to generate high quality evidence regarding the efficacy of PHBP resuscitation for trauma patients. Patient-centred outcome measures include survival and morbidity. Physiological and coagulation studies will add to understanding of the mechanisms underlying trauma resuscitation. Logistic considerations will aid future service planning if a benefit to patients is demonstrated.

The RePHILL trial opened to recruitment in December 2016. In June 2017, the funder (NIHR Efficacy and Mechanism Evaluation) confirmed successful completion of the pilot phase and agreed that the trial could progress into the main Phase III RCT. As of 01 August 2017, 34 patients had been recruited into the trial.

Study Documents, Administration, Funding and Registration

The full trial Protocol and related documents are available at:

www.birmingham.ac.uk/rephill

Trial Registration

ISRCTN registry identifier: ISRCTN62326938, assigned 11 July 2016

EudraCT registration: 2015-001401-13

MHRA Clinical Trials Authorisation: 16719/0228/001-0001

Research Ethics Committee Approval: South Central - Oxford C, ref: 15/SC/0691

Funding: The RePHILL Trial is supported by the National Institute for Health Research Efficacy and Mechanism Evaluation Programme, grant number 14/152/14. GDP is supported as a NIHR Senior Investigator and Director of Research for the Intensive Care Foundation

Sponsor: University Hospitals Birmingham NHS Foundation Trust (RRK5174)

The Sponsor and Funder provided feedback during study design. The RePHILL Trial Collaborators are responsible for study design and for data collection, processing, analysis and interpretation. The decision to submit the final report lies exclusively with the Trial Management Group.

RePHILL Trial Collaborators:

The authors gratefully acknowledge the contributions made by the remaining

RePHILL Trial Collaborators:

NHS Blood and Transplant

Derbyshire, Leicestershire & Rutland Air Ambulance

East Anglian Air Ambulance

Essex and Hertfordshire Air Ambulance Trust

MAGPAS Helimedix

Midlands Air Ambulance

Warwickshire & Northamptonshire Air Ambulance

Essex Voluntary Blood Service

Leicestershire & Rutland Blood Bikes

Midlands Freewheelers

SERV Norfolk

SERV Suffolk & Cambridge

Warwickshire & Solihull Blood Bikes

East of England Ambulance Service NHS Trust

West Midlands Ambulance Service NHS Foundation Trust

Barts Health NHS Trust

Cambridge University Hospitals NHS Foundation Trust

Colchester Hospital University NHS Foundation Trust

Norfolk & Norwich University Hospitals NHS Foundation Trust

North Bristol NHS Foundation Trust

Nottingham University Hospitals NHS Trust

The Royal Wolverhampton NHS Trust

Sheffield Teaching Hospitals NHS Foundation Trust

University Hospitals Birmingham NHS Foundation Trust

University Hospitals Coventry and Warwickshire NHS Trust

University Hospitals of North Midlands NHS Trust

Acknowledgements

The authors thank the East of England Trauma Network, Dorset & Somerset Air Ambulance, Ms Amisha Desai (Clinical Trials Pharmacist, University Hospitals Birmingham NHS Foundation Trust), Dr Karen Piper (Programme Manager, NIHR SRMRC), Dr Victoria Day (Clinical Research Grant Coordinator, UHB), Dr Alison Harte (Clinical Research Officer, UHB), Ms Lauren Cooper (NIHR SRMRC), Dr Paul Harrison (Institute of Inflammation and Aging, University of Birmingham), Mrs Hannah Watson (Data Manager, BCTU), Mr Nicholas Hilken, Mr Darren Douglas and Mr Anthony Prigg (IT Programmers, BCTU), Mrs Manjit Tandy (Senior Trial Coordinator, BCTU) and Mr David Smith (Bristol Hospital Liaison Committee for Jehovah's Witnesses) for their input into the design and preparation of this study.

Contributions:

MJM and NC were the original co-principal investigators and oversaw and actively participated in all aspects of trial design and implementation and, together with HD, IMS, NI, JRB, AMcL, MG and GDP, constructed the original study design and

contributed to funding applications. GDP has subsequently succeeded MJM as co-principal investigator. IMS drafted the funding applications, protocol and application for ethical review. All authors contributed to protocol development and/or application for ethical review. HD and MH established and validated the procedures for PHBP supply. GDP provided the ethical framework for consent. JRB and NI wrote the statistical analysis plan. NI, MG and GS developed the protocol to allow implementation. GS drafted the patient information sheets, informed consent forms and case report forms, and has managed the site set-up processes. MJM, NC, AMcL, JMH, HD and DNN are involved in implementing the trial. IMS wrote the main manuscript. All authors contributed to the writing of the manuscript and agreed with submission of the final version for publication. All authors contributed to the writing of the manuscript and agreed with submission of the final version for publication.

Competing Interests: The authors declare no conflicts of interest.

REFERENCES

The Medicines for Human Use (Clinical Trials) Regulations 2004. United Kingdom.

The Blood Safety and Quality Regulations 2005. United Kingdom.

The Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants) Regulations 2006. United Kingdom.

The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. United Kingdom.

Advisory Committee on the Safety of Blood, Tissues and Organs. (2013) *Importation of plasma as a vCJD risk reduction measure: reconsideration of "acceptable" source countries*. London: Crown Copyright. Available from:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192586/Plasma_sourcing_paper_final_version.pdf [Accessed on 22 Dec 2014]

Bhangu, A., Nepogodiev, D., Doughty, H. & Bowley, D.M. (2013) Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. *Injury*, **44**, 1693-1699.

Bolton-Maggs, P.H. (2015) Conference report: the 2015 SHOT symposium and report - what's new? *Transfusion Medicine*, **25**, 295-298.

Bolton-Maggs, P.H.B., New, H.V. & Tinegate, H. (2016) Use of and reactions to fresh frozen plasma in the UK. *ISBT Science Series*, **11**, 133-139.

Brown, J.B., Guyette, F.X., Neal, M.D., Claridge, J.A., Daley, B.J., Harbrecht, B.G., Miller, R.S., Phelan, H.A., Adams, P.W., Early, B.J., Peitzman, A.B., Billiar, T.R. & Sperry, J.L. (2015a) Taking the Blood Bank to the Field: The Design and Rationale

of the Prehospital Air Medical Plasma (PAMPer) Trial. *Prehospital Emergency Care*, **19**, 343-350.

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

Bux, J., Dickhorner, D. & Scheel, E. (2013) Quality of freeze-dried (lyophilized) quarantined single-donor plasma. *Transfusion*, **53**, 3203-3209.

Chan, A.-W., Tetzlaff, J.M., Altman, D.G., Laupacis, A., Gotzsche, P.C., Krleza-Jeric, K., Hrobjartsson, A., Mann, H., Dickersin, K., Berlin, J.A., Dore, C.J., Parulekar, W.R., Summerskill, W.S.M., Groves, T., Schulz, K.F., Sox, H.C., Rockhold, F.W., Rennie, D. & Moher, D. (2013) SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine*, **158**, 200-207.

Dalton, A.M. (1993) Use of blood transfusions by helicopter emergency medical services: is it safe? *Injury*, **24**, 509-510.

del Junco, D.J., Holcomb, J.B., Fox, E.E., Brasel, K.J., Phelan, H.A., Bulger, E.M., Schreiber, M.A., Muskat, P., Alarcon, L.H., Cohen, M.J., Cotton, B.A., Wade, C.E., Myers, J.G., Rahbar, M.H. & the PROMMTT Study Group. (2013) Resuscitate early with plasma and platelets or balance blood products gradually: findings from the PROMMTT study. *The Journal of Trauma and Acute Care Surgery*, **75**, S24-S30.

DRK-Blutspendedienst West. (2017) *LyoPlas N-w: Safety and Compatibility*. Hagen: DRK-Blutspendedienst West. Available from: <https://www.blutspendedienst->

west.de/ueber_uns/zentren_einrichtungen/plasma_en/informationen_fuer_kliniken_aerzte/sicherheit_vertraeglichkeit.php [Accessed on 07 Oct 2017]

Dunbar, N.M., Yazer, M.H. & Biomedical Excellence for Safer Transfusion Collaborative. (2016) A possible new paradigm? A survey-based assessment of the use of thawed group A plasma for trauma resuscitation in the United States. *Transfusion*, **56**, 125-129.

Ferreira-Gonzalez, I., Permanyer-Miralda, G., Busse, J.W., Bryant, D.M., Montori, V.M., Alonso-Coello, P., Walter, S.D. & Guyatt, G.H. (2007) Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *Journal of Clinical Epidemiology*, **60**, 651-657.

Glassberg, E., Nadler, R., Gendler, S., Abramovich, A., Spinella, P.C., Gerhardt, R.T., Holcomb, J.B. & Kreiss, Y. (2013) Freeze-dried plasma at the point of injury: from concept to doctrine. *Shock*, **40**, 444-450.

Gokhale, S.G., Scorer, T. & Doughty, H. (2016) Freedom from frozen: the first British military use of lyophilised plasma in forward resuscitation. *Journal of the Royal Army Medical Corps*, **162**, 63-65.

Hasler, R.M., Nuesch, E., Juni, P., Bouamra, O., Exadaktylos, A.K. & Lecky, F. (2011) Systolic blood pressure below 110mmHg is associated with increased mortality in blunt major trauma patients: Multicentre cohort study. *Resuscitation*, **82**, 1202-1207.

Hasler, R.M., Nuesch, E., Juni, P., Bouamra, O., Exadaktylos, A.K. & Lecky, F. (2012) Systolic blood pressure below 110 mmHg is associated with increased

mortality in penetrating major trauma patients: Multicentre cohort study.

Resuscitation, **83**, 476-481.

Holcomb, J.B., del Junco, D.J., Fox, E.E., Wade, C.E., Cohen, M.J., Schreiber, M.A., Alarcon, L.H., Bai, Y., Brasel, K.J., Bulger, E.M., Cotton, B.A., Matijevic, N., Muskat, P., Myers, J.G., Phelan, H.A., White, C.E., Zhang, J., Rahbar, M.H. & Group, P.S.

(2013) The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surgery*, **148**, 127-136.

Holcomb, J.B., Donathan, D.P., Cotton, B.A., Del Junco, D.J., Brown, G., Wenckstern, T.V., Podbielski, J.M., Camp, E.A., Hobbs, R., Bai, Y., Brito, M., Hartwell, E., Duke, J.R. & Wade, C.E. (2015a) Prehospital Transfusion of Plasma and Red Blood Cells in Trauma Patients. *Prehospital Emergency Care*, **19**, 1-9.

Holcomb, J.B., Tilley, B.C., Baraniuk, S., Fox, E.E., Wade, C.E., Podbielski, J.M., del Junco, D.J., Brasel, K.J., Bulger, E.M., Callcut, R.A., Cohen, M.J., Cotton, B.A., Fabian, T.C., Inaba, K., Kerby, J.D., Muskat, P., O'Keeffe, T., Rizoli, S., Robinson, B.R.H., Scalea, T.M., Schreiber, M.A., Stein, D.M., Weinberg, J.A., Callum, J.L., Hess, J.R., Matijevic, N., Miller, C.N., Pittet, J.-F., Hoyt, D.B., Pearson, G.D., Leroux, B., van Belle, G. & the PROPPR Study Group. (2015b) Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*, **313**, 471-482.

Holcomb, J.B. (2017) Major scientific lessons learned in the trauma field over the last two decades. *PLoS Medicine*, **14**, e1002339.

Holcomb, J.B., Swartz, M.D., DeSantis, S.M., Greene, T.J., Fox, E.E., Stein, D.M., Bulger, E.M., Kerby, J.D., Goodman, M., Schreiber, M.A., Zielinski, M.D., O'Keeffe, T., Inaba, K., Tomasek, J.S., Podbielski, J.M., Appana, S.N., Yi, M., Wade, C.E. & Group, P.S. (2017) Multicenter observational prehospital resuscitation on helicopter study. *Journal of Trauma and Acute Care Surgery*, **83**, S83-S91.

Hunt, B.J., Allard, S., Keeling, D., Norfolk, D., Stanworth, S.J., Pendry, K. & British Committee for Standards in, H. (2015) A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology*, **170**, 788-803.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996) *Guideline for Good Clinical Practice*. Geneva: ICH Secretariat. Available from:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [Accessed on 09 July 2017]

Jenkins, D., Rappold, J.F., Badloe, J.F., Berseus, O., Blackbourne, L., Brohi, K.H., Butler, F.K., Cap, A.P., Cohen, M.J., Davenport, R., DePasquale, M., Doughty, H., Glassberg, E., Hervig, T., Hooper, T.J., Kozar, R., Maegele, M., Moore, E.E., Murdock, A., Ness, P.M., Pati, S., Rasmussen, T., Sailliol, A., Schreiber, M.A., Sunde, G.A., van de Watering, L.M., Ward, K.R., Weiskopf, R.B., White, N.J., Strandenes, G. & Spinella, P.C. (2014a) Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. *Shock*, **41 Suppl 1**, 3-12.

Jenkins, D., Stubbs, J., Williams, S., Berns, K., Zielinski, M., Strandenes, G. & Zietlow, S. (2014b) Implementation and Execution of Civilian Remote Damage Control Resuscitation Programs. *Shock*, **41 Suppl 1**, 84-89.

Joint UKBTS/NIBSC Professional Advisory Committee. (2010) *Minutes of 45th Meeting*. Available from: http://www.transfusionguidelines.org/document-library/documents/jpac-meeting-minutes-11-march-2010/download-file/gi_jpac-minutes_2010-03-11.pdf [Accessed on 19 December 2015]

Jost, D. & Lanoe, V. (2017) *Pre-hospital Administration of Lyophilized Plasma for Post-traumatic Coagulopathy Treatment (PREHO-PLYO)* Bethesda: National Institutes of Health. Available from: <https://clinicaltrials.gov/ct2/show/NCT02736812> [Accessed on 06 Jul 2017]

Kerwin, A.J., Haut, E.R., Burns, J.B., Como, J.J., Haider, A., Stassen, N., Dahm, P. & Eastern Association for the Surgery of Trauma Practice Management Guidelines Ad Hoc Committee. (2012) The Eastern Association of the Surgery of Trauma approach to practice management guideline development using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. *Journal of Trauma and Acute Care Surgery*, **73**, S283-287.

Kotwal, R.S., Howard, J.T., Orman, J.A., Tarpey, B.W., Bailey, J.A., Champion, H.R., Mabry, R.L., Holcomb, J.B. & Gross, K.R. (2016) The effect of a Golden Hour policy on the morbidity and mortality of combat casualties. *JAMA Surgery*, **151**, 15-24.

Martinaud, C., Ausset, S., Deshayes, A.V., Cauet, A., Demazeau, N. & Sailliol, A. (2011) Use of freeze-dried plasma in French intensive care unit in Afghanistan. *Journal of Trauma-Injury Infection & Critical Care*, **71**, 1761-1764.

Moore, E.E., Chin, T.L., Chapman, M.C., Gonzalez, E., Moore, H.B., Silliman, C.C., Hansen, K.C., Sauaia, A. & Banerjee, A. (2015) Plasma first in the field for postinjury hemorrhagic shock. *Shock*, **41**, 35-38.

Murad, M.H., Stubbs, J.R., Gandhi, M.J., Wang, A.T., Paul, A., Erwin, P.J., Montori, V.M. & Roback, J.D. (2010) The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion*, **50**, 1370-1383.

National Institute for Health and Clinical Excellence. (2016) *Major Trauma: assessment and initial management*. London: National Clinical Guideline Centre.

Neal, M.D., Hoffman, M.K., Cuschieri, J., Minei, J.P., Maier, R.V., Harbrecht, B.G., Billiar, T.R., Peitzman, A.B., Moore, E.E., Cohen, M.J. & Sperry, J.L. (2012) Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. *Journal of Trauma and Acute Care Surgery*, **72**, 892-898.

NHS Blood and Transplant. (2014) *Blood Group Basics*. Watford: NHS Blood and Transplant. Available from: <http://www.blood.co.uk/about-blood/blood-group-basics/> [Accessed on 10 January 2015]

O'Reilly, D.J., Morrison, J.J., Jansen, J.O., Nordmann, G., Rasmussen, T.E., Midwinter, M.J. & Doughty, H. (2014a) Initial UK experience of prehospital blood transfusion in combat casualties. *Journal of Trauma and Acute Care Surgery*, **77**, S66-S70.

O'Reilly, D.J., Morrison, J.J., Jansen, J.O., Apodaca, A.N., Rasmussen, T.E. & Midwinter, M.J. (2014b) Prehospital blood transfusion in the en route management of severe combat trauma: A matched cohort study. *Journal of Trauma and Acute Care Surgery*, **77**, S114-S120.

Perkins, G., Gates, S. & The PARAMEDIC-2 Investigators Group. (2015) *PARAMEDIC-2: The Adrenaline Trial: Protocol*. Warwick: Warwick Medical School

Clinical Trials Unit. Available from:

http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/critical/paramedic2/documents/protocol_1.1_24_june_2015.pdf [Accessed on 01 September 2015]

Rajasekhar, A., Gowing, R., Zarychanski, R., Arnold, D.M., Lim, W., Crowther, M.A. & Lottenberg, R. (2011) Survival of trauma patients after massive red blood cell transfusion using a high or low red blood cell to plasma transfusion ratio. *Critical Care Medicine*, **39**, 1507-1513.

Regnier, M.-A., Raux, M., Le Manach, Y., Asencio, Y., Gaillard, J., Devilliers, C., Langeron, O. & Riou, B. (2012) Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology*, **117**, 1276-1288.

Reynolds, P.S., Michael, M.J., Cochran, E.D., Wegelin, J.A. & Spiess, B.D. (2015) Prehospital use of plasma in traumatic hemorrhage (The PUPATH Trial): study protocol for a randomised controlled trial. *Trials*, **16**, 321.

Sailliol, A., Martinaud, C., Cap, A.P., Civadier, C., Clavier, B., Deshayes, A.-V., Mendes, A.-C., Pouget, T., Demazeau, N., Chueca, M., Martelet, F.-R. & Ausset, S. (2013) The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service. *Transfusion*, **53** 65S-71S.

Schoenfeld, H., Pruss, A., Keller, M., Schuster, M., Meinck, K., Neuner, B. & von Heymann, C. (2010) Lyophilised plasma: evaluation of clotting factor activity over 6 days after reconstitution for transfusion. *Journal of Clinical Pathology*, **63**, 726-730.

Schulz, K.F., Altman, D.G., Moher, D. & the Consort Group. (2011) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery*, **9**, 672-677.

Shackelford, S.A. (2017) Prehospital blood product use and improved outcomes. Paper presented at: *Remote Damage Control Resuscitation symposium of the Trauma Hemostasis and Oxygenation Research Network*, Os, Norway. June 26.

Shlaifer, A., Siman-Tov, M., Radomislensky, I., Peleg, K., Shina, A., Baruch, E.N., Glassberg, E. & Yitzhak, A. (2017) Prehospital administration of freeze-dried plasma, is it the solution for trauma casualties? *Journal of Trauma and Acute Care Surgery*, **83**, 675-682.

Smith, I.M., James, R.H., Dretzke, J. & Midwinter, M.J. (2016) Prehospital Blood Product Resuscitation for Trauma: A Systematic Review. *Shock*, **46**, 3-16.

Stanworth, S.J., Davenport, R., Curry, N., Seeney, F., Eaglestone, S., Edwards, A., Martin, K., Allard, S., Woodford, M., Lecky, F.E. & Brohi, K. (2016) Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *British Journal of Surgery*, **103**, 357-365.

Sunde, G.A., Vikenes, B., Strandenes, G., Flo, K.C., Hervig, T.A., Kristoffersen, E.K. & Heltne, J.K. (2015) Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. *Journal of Trauma and Acute Care Surgery*, **78**, S26-S30.

Wales Air Ambulance. (2015) *New kit & blood on board*. Swansea: Wales Air Ambulance. Available from: <http://walesairambulance.com/en/new-kit-blood-on-board> [Accessed on 25 June 2015]

Weaver, A.E., Eshelby, S., Norton, J. & Lockey, D.J. (2013) The introduction of on-scene blood transfusion in a civilian physician-led pre-hospital trauma service. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **21**, S27.

World Medical Association. (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*, **310**, 2191-2194.

Zielinski, M.D., Stubbs, J.R., Berns, K.S., Glassberg, E., Murdock, A.D., Shinar, E., Sunde, G.A., Williams, S., Yazer, M.H., Zietlow, S. & Jenkins, D.H. (2017) Prehospital blood transfusion programs: Capabilities and lessons learned. *Journal of Trauma and Acute Care Surgery*, **82**, S70-S78.