BMJ Open

Effect of early cryoprecipitate transfusion versus standard care in women who develop severe postpartum haemorrhage (ACROBAT) in the UK: a protocol for a pilot cluster randomised trial

Laura Green ,[1,2,3] Jahnavi Daru ,[4] Julie Dodds ,[4] Francisco Jose Gonzalez Carreras ,[4] Doris Lanz ,[4] Javier Zamora ,[4,5] Maria del Carmen Pardo Llorente ,[6] Teresa Pérez Pérez ,[7] Lorna Sweeney ,[8] Shakila Thangaratinam ,[4,9] Amy Thomas,[10] Khalid Saeed Khan [4]

To cite: Green L, Daru J, Dodds J, *et al*. Effect of early cryoprecipitate transfusion versus standard care in women who develop severe postpartum haemorrhage (ACROBAT) in the UK: a protocol for a pilot cluster randomised trial. *BMJ Open* 2020;**10**:e036416. doi:10.1136/bmjopen-2019-036416

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-036416).

Received 13 December 2019
Revised 03 April 2020
Accepted 20 May 2020

For numbered affiliations see end of article.

Correspondence to
Dr Laura Green;
Laura.Green27@nhs.net

ABSTRACT

Introduction The incidence of severe postpartum haemorrhage (PPH) that requires blood transfusion is on the increase. Fibrinogen levels have been shown to drop early and significantly during PPH, which is associated with worse outcomes. Early fibrinogen replacement could potentially improve outcomes. No studies have investigated the clinical impact of early cryoprecipitate transfusion in PPH. Prior to performing a full-scale trial, a pilot study is needed to determine feasibility of the intervention and recruitment.

Methods ACROBAT is a cluster-randomised pilot study with a qualitative evaluation. Four large London maternity units are randomised to either the intervention or control group. The intervention group will adapt their major obstetric haemorrhage procedures to administer cryoprecipitate early for primary PPH. The control group will retain their standard of care.

We include women at >24 weeks gestation who are actively bleeding within 24 hours of delivery and for whom transfusion of red blood cells (RBCs) has been started. We exclude women who decline blood transfusions in advance or have inherited Factor XIII or fibrinogen deficiency. Due to the emergency nature of the intervention, informed consent for administering the intervention is waived.

The primary objective is to assess the feasibility of administering cryoprecipitate within 90 min of RBC request, as compared with standard treatment where cryoprecipitate is given later or not at all. Secondary objectives include the feasibility of recruitment and data collection, reasons for and barriers to consent, preliminary maternal clinical outcomes, identification of the optimal infrastructure pathways for study delivery, and acceptability of the intervention and outcomes.

Ethics and dissemination The trial has approvals from the London—Brighton & Sussex Research Ethics Committee (ref. 18/LO/2062), the Confidentiality Advisory Group (ref. 18/CAG/0199) and Health Research Authority (IRAS number 237959). Data analysis and publication of manuscripts will start in Q3 2020.

Trial registration number ISRCTN12146519.

Strengths and limitations of this study

- This is the first randomised controlled trial (RCT) assessing the early administration of cryoprecipitate compared with standard care in severe postpartum haemorrhage (PPH).
- We have chosen a pilot cluster RCT design rather than an individually randomised study to assess if it is feasible to administer cryoprecipitate early during PPH, to avoid contamination, but this could be seen as a limitation.
- In this study, we have obtained substantial input from patient and public members into the consent processes, and our nested qualitative evaluation will explore how the consent materials and processes are received by participating women and healthcare professionals.
- In this study, we will also survey various stakeholders (patient representatives and various clinical specialists) to prioritise outcome measures that should be reported in future trials for treatment of severe PPH.

INTRODUCTION

Postpartum haemorrhage (PPH) is a common cause of mortality, morbidity and long-term disability worldwide.[1] The incidence of severe PPH that requires treatment with blood transfusion has increased in the UK, due to increasing maternal age, obesity, increased obstetric intervention and higher rates of

caesarean section.[2] The increase in PPH incidence has seen a significant rise in the maternal morbidity rate, with severe PPH accounting for ~77% of all maternal intensive care unit admissions between 2003 and 2012.[3] Further, women who survive severe PPH are likely to suffer more long-term morbidity compared with other types of obstetric complications.[4]

Several studies have demonstrated consistently that fibrinogen levels drop early and significantly during PPH and that a low level of fibrinogen (<2 g/L) is an independent predictor for morbidity[5] and requirement for additional red blood cell (RBC) transfusion.[6 7] Despite this, a UK study of women with PPH who had received massive transfusion (≥8 RBC units) showed that only 60% of women were administered cryoprecipitate, and this was given after a mean of eight RBC units transfusion.[8] The benefits of early correction of coagulation abnormalities (of which fibrinogen is part) in patients with bleeding have recently been demonstrated by several trials.[9–11] However, to date, there have been no clinical trials to validate if early replacement of fibrinogen with cryoprecipitate in severe PPH is better than the current standard, where cryoprecipitate is given if fibrinogen levels drop to <2 g/L or if the woman receives massive transfusion.[12] The reasons for this include the delay in obtaining blood results and the practical limits of how quickly cryoprecipitate can be administered to patients, considering the thawing and transportation time. A more proactive approach to correct fibrinogen early, by administering cryoprecipitate as soon as the need for transfusion is identified, may improve outcomes for women. However, prior to performing a large interventional trial, a pilot study is needed to identify barriers to recruitment, assess feasibility and acceptability of the treatment, and fine-tune study procedures.

METHODS AND ANALYSIS

Design

A cluster-randomised, controlled, non-blinded, pilot trial with additional qualitative evaluation.

Setting

Participants will be recruited at four maternity units within London (UK): the Royal London Hospital, Newham University Hospital, Whipps Cross University Hospital and Homerton University Hospital. Two of these maternity units are randomised to the intervention group and two to the control group (see figure 1).

Objectives and endpoints

Primary objective

To assess the feasibility of administering cryoprecipitate early (within 90 min of request of the first RBC unit) in pregnant women who are actively bleeding and who require blood transfusion for treatment of bleeding within 24 hours of delivery, as compared with standard treatment, where cryoprecipitate is given later or not at all.

Secondary objectives

- To assess the feasibility of recruitment and data collection and the proportion of participants treated according to allocation.
- To assess reasons for consent, or refusal of consent, for data collection.
- To obtain preliminary data on event rates in both intervention and control groups to help estimate the sample size and intracluster correlation, and to estimate the impact of early cryoprecipitate transfusion on clinical outcomes and haemostatic markers, to inform the definitive trial.
- To identify the optimal infrastructure pathway and personnel to deliver the intervention, and to identify and recruit patients in the intervention group within and outside working hours (ie, transfusion laboratory or clinical areas).
- To evaluate the acceptability of the study intervention and outcomes to clinicians and participating women.

Primary endpoint

Proportion of women who were administered cryoprecipitate within 90 min of the request of the first unit of RBC transfusion, in the intervention and control groups. The first request of RBC units will be documented as the time the laboratory is called to request RBC units, or the time when the first unit of RBC is removed from the remote blood fridges (where available).

Secondary endpoints

- Proportion of women who were recruited to the trial, and for whom complete outcomes were obtained.
- Proportion of women who were approached and did not consent to the trial.
- Proportion of women who were approached and agreed to routine data collection.
- Proportion of women where there was a study protocol violation.
- Preliminary clinical outcome data will be collected up to hospital discharge or 28 days after recruitment (whichever is sooner), and these include: mortality (all-cause); hysterectomy; surgical interventions to stop haemorrhage such as, but not limited to, intrauterine balloon tamponade, uterine artery embolisation, uterine artery ligation etc.; the total number of units transfused within 24 hours and until hospital discharge (number of units for RBC, fresh frozen plasma, cryoprecipitate and platelet transfusion); transfusion-related reactions; length of stay in high dependency unit, intensive care units and hospital; requirement for mechanical ventilation; any organ failure; symptomatic thrombotic events (ie, pulmonary embolism, and/or deep vein thrombosis and arterial thrombotic events, and maternal fatigue as

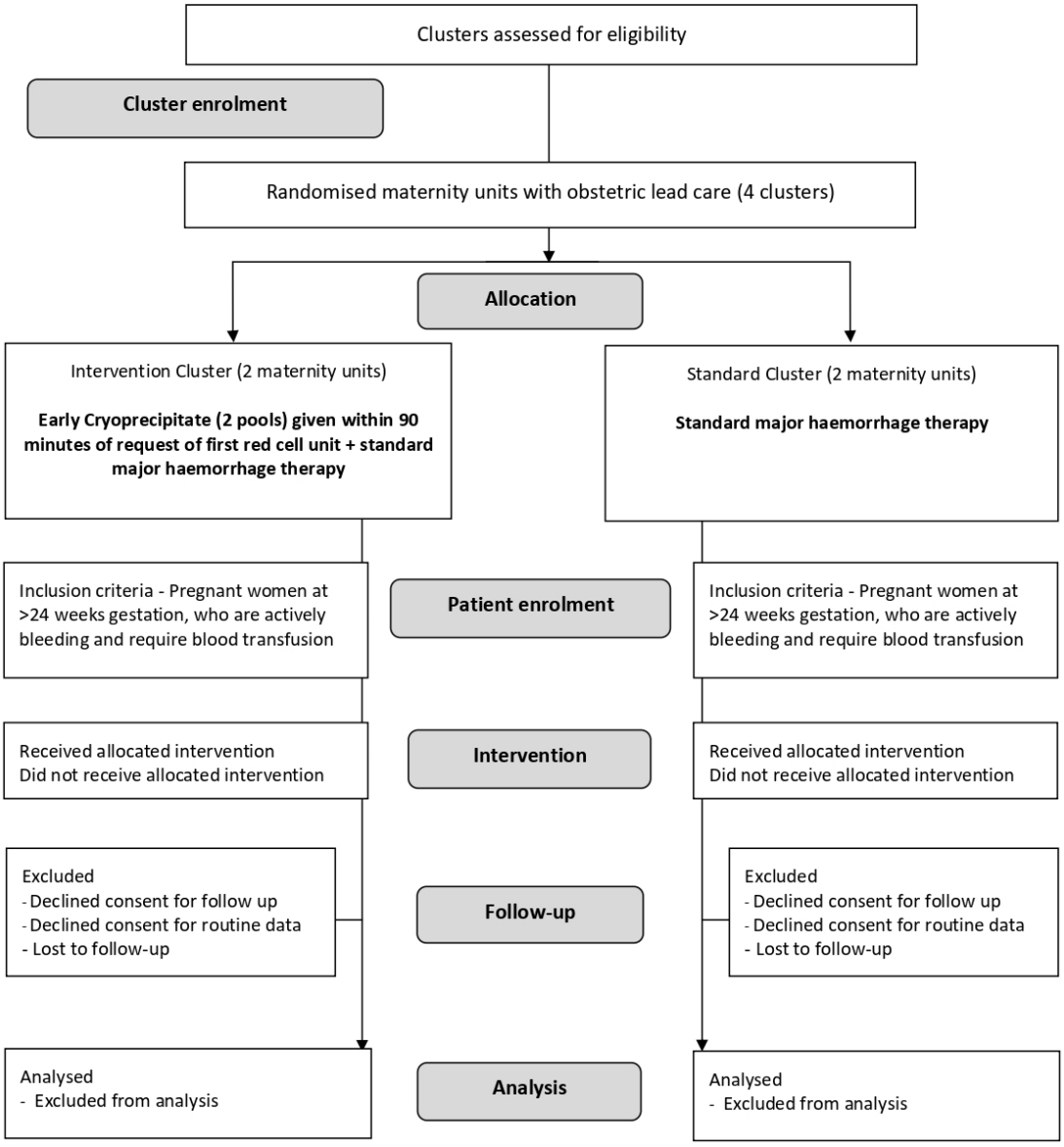

Figure 1 CONSORT flowchart.

measured by the Multidimensional Fatigue Inventory (MFI) questionnaire.

- Occurrence of symptomatic thrombotic events (arterial and venous) up to 3 months after recruitment.

Study population

As this is a cluster randomised controlled trial (RCT), all women who fulfil the inclusion criteria will be treated according to the allocated group in the respective maternity unit.

Inclusion criteria: pregnant women at >24 weeks gestation, who are actively bleeding within 24 hours of delivery and for whom at least one unit of RBC has been started or transfused to stem active bleeding.

Exclusion criteria: women who decline blood transfusion in advance and women with inherited Factor XIII or fibrinogen deficiency. These are routinely treated according to a separate, dedicated protocol.

Recruitment

Consent procedures

Due to the urgency of the intervention, the cluster design and the fact that the occurrence of PPH cannot be adequately predicted, advance consent for administering intervention will be waived. However, women on both groups will be approached by the research team for written, informed consent to collect their routine, de-identified data, up to hospital discharge or 28 days after delivery—whichever is first. In addition to this routine data, they will also be asked for consent to complete the MFI questionnaire; readiness to be contacted for a qualitative interview, collection of residual blood samples from the hospital laboratories; and a follow-up telephone call 3 months post-discharge. For women who die or are discharged from the hospital before being identified and approached for their consent and who cannot

be contacted after discharge, routine, de-identified data will be collected from the medical notes up to hospital discharge or 28 days after delivery—whichever is first. Additionally, assent and parental consent will be obtained for participants under the age of 16 years and consultee consent will be obtained for an eligible woman without the capacity to consent. Women will be informed that they have the right to refuse consent for data collection, as well as to withdraw consent previously given, at any time, without giving a reason, and that this will not affect their subsequent care. If they withdraw consent, data collected up to the point of withdrawal will be retained in the study. Participant information sheets and consent forms used for this pilot study are available as online supplementary files 1-6.

Information posters and leaflets are displayed in antenatal clinics to inform women on each study site. These provide study aims, contact details and sources for further information. All recruitment materials have been developed with significant input from an East London patient and public involvement (PPI) group (see the Discussion section).

Screening procedures

Given the design of the study, eligible women are identified after they have received treatment for PPH. To this end, the research team will consult obstetric transfusion records and delivery records on a daily basis. Additionally, ongoing training and information campaigns for clinical obstetric, anaesthetic and laboratory teams are in place to ensure both treatment adherence and support to the research team in identifying eligible participants.

Randomisation procedures

We will randomly allocate two hospitals each to the intervention and control groups, through randomisation at a ratio of 1:1, prior to the start of recruitment (see figure 1).

Study interventions and assessments

Intervention group: two pools of cryoprecipitate will be thawed as soon as possible by the transfusion laboratory and transfused to eligible women within 90 min of the request of the first RBC unit.

Control group: control group will administer standard transfusion therapy, where cryoprecipitate is administered if the fibrinogen result is <2 g/L, or if a woman has received massive transfusion (ie, >8 RBC transfusion) in accordance with national guidelines.[13 14]

Assessments and data collection: clinical data will be collected from medical notes and records, with the exception of the patient-reported fatigue questionnaire. Case report forms (CRFs) will be completed by the clinical research team on each maternity unit and entered into a bespoke, secure online study database using a unique study ID for each participant.

Qualitative data will be collected through interviews with 10–15 participating women, depending on data saturation, to explore their opinions and experiences of study procedures, ~2–3 months after their recruitment. Where needed, the interviewer will connect women with birth debriefing support structures at the hospital where they gave birth. Additionally, ~10 healthcare professionals involved in the delivery of the study will be interviewed in order to explore perspectives and experiences with the delivery of the intervention. All interviews will be subject to separate written informed consent. Interviews will be audio-recorded, with participant consent, and conducted using an interview schedule.

Follow-up: women will be followed up until discharge or 28 days after delivery, whichever is sooner. Additionally, there will be one follow-up phone call at 3 months post-delivery enquiring about any thromboembolic events, provided that women have given informed consent for follow-up. See table 1 for an overview of intervention and assessments.

Statistics

Sample size calculation

The calculation of the sample size is based on an assumption of the incidence of PPH requiring any blood transfusion being 0.5%–4.5%,[3 15] and for this trial, it was estimated that 2% of the women would be eligible for the pilot. The total number of deliveries at four hospitals is over 24 000 per year, indicating that ~400 women per year will go on to develop PPH and require a blood transfusion.

For the pilot study, 200 eligible women will be recruited, split into ~100 per group. This sample size will enable us to construct a 95% CI for the proportion of women administered cryoprecipitate within 90 min of bleeding onset with a precision ±8 percentage points if the estimated proportion were 0.8, that is, from 0.71 to 0.87, Wilson approach.[16] For the consent rate, given a fixed n=200 and with a p=0.5, the 95% CI will range between 0.43 and 0.57. Although we will aim to recruit 100 women per treatment group, the imbalance between the intervention and control groups can be accommodated. Precisions obtained will be similar even in the extreme scenario in which one arm recruits 140 and the other 60 patients.

Statistical analysis

We will summarise continuous variables using mean and SD or median and IQR as appropriate. We will provide point estimates of proportions for categorical variables along with corresponding exact 95% CI. We will explore differences in recruitment, acceptance and consenting rates between the two groups of the trial but avoid formal statistical tests. Given the limited number of clusters randomised (n=4), it is crucial to assess if there is any systematic selection bias that can be suspected after examining baseline clinical and demographic characteristics of participating women in the intervention and standard care groups. Additionally, this low number of clusters will not be enough to provide a robust estimation of intracluster correlation coefficient (ICC). Thus, the estimation obtained using pilot-trial data will be compared with

Table 1 Schedule of enrolment, interventions and assessments

		Study period			
		Delivery	Post-intervention, pre-discharge		Follow-up
Timepoint	Pre-study	0	0–28 days	Consent* to 28 days	3 months
Enrolment					
Allocation (cluster randomisation)	X				
Eligibility screen			X		
Informed consent			X		
Interventions					
Intervention clusters: 2 pools of early cryoprecipitate		X			
Standard haemorrhage protocol		X			
Assessments					
Demographics and medical history				X	
Documentation of medical and surgical interventions				X	
Clinical outcomes and adverse events				X	
Symptomatic thrombotic events				X	X
Haemostatic markers				X	
MFI questionnaire				X	
Qualitative interviews					X

*Alternatively, if conditions for waiver are fulfilled, routine data can be collected in the absence of written informed consent.
MFI, multidimensional fatigue inventory.

ICC estimations available in the literature. The analysis of clinical outcomes will only be exploratory, and we will avoid formal statistical tests to compare the two groups. We will also focus on assessing data collection procedures, to obtain an estimation of data quality and the degree of missingness.

Progression criteria

Table 2 below outlines the main criteria that will be considered to assess the feasibility of a full-scale RCT. In addition, our qualitative findings will also be used to support the decision-making around progression to a full-scale trial. For example, if a progression criterion outlined in table 2 does not meet the threshold for progression, but we have developed a qualitative understanding of why this occurred and how it could be improved, then it may still be possible to proceed with the full trial.

Table 2 Progression criteria

Feasibility objectives and related data to be collected	Go criteria to proceed to full trial	Criteria to reassess and adjust full trial protocol	Stop criteria
Study population			
1. Consent rates of eligible women	Rate >25% of eligible women agreeing to participate.	Rate between 11% and 24% women agreeing to participate	Rate <10% of eligible women agreeing to participate
Study outcomes			
2. Proportion of women in either intervention or control group for whom the allocated treatment is adhered to.	Adherence to allocated treatment in >80% of study sample.	Adherence to allocated treatment in between 51% and 79% of study sample.	Adherence to allocated treatment in <50% of study sample.
RCT processes			
3. Collection of data on clinical outcomes.	Complete data available of >80% of study sample.	Missing data between 21% and 49% of study sample.	Data missing of >50% of study sample.

RCT, randomised controlled trial.

Trial management and oversight

Data management

All data management will be undertaken by the Queen Mary University of London (QMUL). Standard operating procedures will be in place for the collection and handling of data. All study data will be entered directly by trained and delegated local research staff into a secure, bespoke electronic trial database set up and hosted by epiGenesys, University of Sheffield. User accounts will be allocated and managed centrally by the trial coordinator and restricted to appropriate site level access. Data collected on the forms and entered onto the electronic database will only identify the participants by a unique trial number. No identifiable data will be stored on the trial database.

Trial management

The trial is managed and run by the Barts Research Centre for Women's Health trials office at QMUL. The trials office is responsible for safety reporting, coordination of trial committees, statistical analysis and reporting, trial monitoring, database management and case report form design.

Trial oversight

The project steering committee (PSC) has been established to oversee and monitor the trial conduct and patient safety. The committee is chaired by an independent consultant anaesthetist (Dr Matthew Wilson, University of Sheffield), with four other independent members, including a consultant obstetrician (Prof Asma Khalil), a consultant haematologist (Dr Susan Robinson), a statistician (Mr Baptiste Leurent) and a lay representative (Ms Ngawai Moss). The PSC provides overall supervision of the trial and ensures that it is being conducted according to the protocol, good clinical practice and relevant regulations. This committee also monitors trial progress in relation to recruitment, data capture and completeness, protocol adherence and deviations and subject withdrawals. The committee meets every 6 months. The PSC is also responsible for reviewing the trial data throughout the study and assessing whether there are any safety issues that need to be brought to the attention of the sponsor, or any ethical reasons why the trial should not continue. Given the low risk of the study intervention and that it is non-blinded, no separate data safety monitoring committee will be established. The sponsor retains the right to audit the study, including any study site or central facility.

Safety reporting

In addition to adverse maternal outcomes specified as secondary clinical outcomes, other adverse events will be documented from intervention to discharge using CRFs. Any events fulfilling the criteria for seriousness (fatal, life-threatening, prolonging hospitalisation, resulting in persistent or significant disability or incapacity) will be reported to the central trials office within 24 hours of the site becoming aware of the event. Exceptions to the requirement for reporting as serious adverse events (SAEs) have been formulated due to the nature of the condition: hospitalisations of fewer than seven nights are not reportable as prolongations, and PPH and pre-eclampsia do not require SAE reporting. We will also exclude events not directly related to the mother's medical care (such as prolonged hospital stay of the mother due to the baby's admission to intensive care or due to social reasons). SAEs will be reviewed by the chief investigator and summarised in reports to the PSC and the research ethics committee (REC). Any SAEs that is considered related to the intervention and that are unexpected will be reported to the sponsor and REC within expedited timelines.

Patient and public involvement

Due to the trial design, the inability to predict in advance many of the women that experience a PPH, and the fact that obtaining consent at the time of bleeding could delay a life-saving treatment, we opted for a waiver of advance consent to administering intervention. Prior to adopting this consent model, we consulted with Katie's Team, a well-established East London women's health PPI group[17] to discuss various aspects of this trial and in particular the timing of consent and the level of information deemed appropriate for antenatal discussion. After deliberation, the PPI group accepted that full advance consent would cause unnecessary anxiety to women and their families, as the majority of women admitted for delivery would not experience severe haemorrhage requiring blood transfusion support. Since the risk associated with administering cryoprecipitate are very low, and cryoprecipitate is already part of standard care (although later on in the course of bleeding), most PPI representatives accepted that full consent postintervention would be appropriate. The group did suggest that advertising the trial through displaying posters and leaflets in antenatal clinics would allow interested women to learn about the study, provide an opportunity to discuss the study with the research team and/or read the study leaflet prior to admission into hospital for delivery. PPI members also gave valuable input on wording and presentation of information (including a graphical representation of the intervention), helping to develop a more patient-centred patient information sheet. The qualitative research embedded within this pilot study will prove integral in evaluating how the consent materials and processes were received in practice.

DISCUSSION

No RCT has previously assessed early cryoprecipitate transfusion in severe PPH in comparison with standard care.[18] In this trial, we chose to perform a cluster RCT rather than an individually randomised study for several reasons. The first is the risk of contamination whereby a patient who is randomised to standard treatment might end up receiving the intervention because it has been made available through the introduction of the research protocol and affected physician equipoise. Second, in the UK maternity units, the management of severe PPH is heavily protocolised and is delivered by a variety of medical staff including midwives, obstetricians, anaesthetists and theatre staff.

Hence, a cluster RCT, where recruiting centres adopt a clearly defined protocol for emergency management, which is uniform across an entire obstetric unit, offers the best way to answer our question without compromising care in an emergency situation.

The sample size of the cluster in a pilot stage is another important factor to consider. It will allow us to estimate the 95% CIs with a precision of ±8 percentage points. Once these CIs are obtained it will be possible to decide whether it is feasible to deliver cryoprecipitate early, so as to upscale to a full trial. Since our primary outcome is to determine whether we can administer cryoprecipitate within 90 min in the intervention arm, the hospitals participating in the feasibility study were selected for the following reasons: (1) they are busy obstetric units catering for a diverse population of pregnant women; (2) they have varying distances between transfusion laboratories and labour wards which would affect the speed of delivering blood components to women experiencing obstetric haemorrhage, and thus test different transfusion systems and infrastructure; and finally (3) all are research-active institutions with the capacity to deliver a trial within an emergency setting. Furthermore, prior to initiating this study, transfusion major haemorrhage protocols on all sites were assessed and all sites were following the national guidelines.[12 13]

In a future full-scale trial, there are many potentially relevant primary outcomes that can be used, and our pilot study results will aid in identifying outcomes for a future trial that are both meaningful and feasible to collect reliably. In addition, our group is also surveying various stakeholders (including patient representatives as well as various clinical specialists) to prioritise outcomes for future trials for the treatment of severe PPH requiring transfusion; this is work ongoing in parallel to this study.

Trial status

Protocol version 4.0, 6 September 2019. The start date of participant recruitment: 4 March 2019. The project recruitment completion date: 29 February 2020. The end of follow-up: 31 May 2020.

ETHICS AND DISSEMINATION

The trial was granted NHS Research Ethics approval from the London—Brighton & Sussex Research Ethics Committee (reference number 18/LO/2062), the Confidentiality Advisory Group for access to and collection of data without prior consent (reference number 18/CAG/0199) and Health Research Authority approval (IRAS number 237959). All subjects participating in the trial will provide written informed consent where possible as highlighted in the methods section above. Specific exceptions to this have been approved by the Confidentiality Advisory Group. Any changes to the protocol are subject to a formal amendment and may not be implemented prior to the approval by the Research Ethics Committee.

Consent for publication

All relevant data from this study will be submitted to peer-reviewed journals for publication following the completion of the study in line with sponsor publication policy. Data will be captured for all study participants, and no patient identifiable data will be used in any publications. The sponsor retains the right to review all publications prior to submission or publication. Responsibility for ensuring accuracy of any publication from this study is delegated to the chief investigator. Authorship will be assigned in compliance with International Committee of Medical Journal Editors (ICMJE) guidelines.

Author affiliations
[1]Blizard Institute, Queen Mary University of London, London, UK
[2]Components, NHS Blood and Transplant, London, UK
[3]Department of Haematology, Barts Health NHS Trust, London, UK
[4]Barts Research Centre for Women's Health (BARC), Institute of Population Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[5]Clinical Biostatistics Unit, Hospital Ramón y Cajal (IRYCIS), CIBER Epidemiology and Public Health, Madrid, Spain
[6]Department of Statistics and Operational Research, Complutense University of Madrid, Madrid, Spain
[7]Department of Statistics and Data Science, Complutense University of Madrid, Madrid, Spain
[8]Institute for Health and Human Development, University of East London, London, UK
[9]WHO Collaborating Centre for Global Women's Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[10]Department of Women's and Neonatal Health, Royal London Hospital, Barts Health NHS Trust, London, UK

Twitter Laura Green @LGreenBartsNHS, Jahnavi Daru @JDaru, Julie Dodds @JuliePDodds, Francisco Jose Gonzalez Carreras @topacurro, Javier Zamora @JavierZa67, Lorna Sweeney @lorna_sweeney, Shakila Thangaratinam @thangaratinam and Khalid Saeed Khan @Profkkhan

Acknowledgements We acknowledge the support of the Joint Research Management Office, Queen Mary University of London as sponsor for the study. Sponsor contact: Head of Research Resources, Joint Research Management Office, Queen Mary University of London, research.governance@qmul.ac.uk. We would like to acknowledge the Barts Health NHS Trust and Homerton University Hospital maternity research teams and their Principal/Local lead Investigators (Dr Tabitha Tanqueray; Homerton University Hospital; Dr Susanna Crowe, Royal London Hospital; Dr Georgina Cubas, Newham University Hospital; Dr Sajith Philip, Whipps Cross University Hospital) for their input in the planning of the practicalities of the study, and Dr Abbas Zaidi for his input into planning and early conduct of the study.We also acknowledge and are grateful for the contributions by members of Katie's Team, the East London women's health research patient and public advisory group.

Contributors LG, KSK, JZ and DL designed the study and LG, JDa and DL wrote the drafts of the manuscript. LS designed the qualitative aspects of the study. FJGC, MdCPL and TPP provided statistical analysis. All authors, including JDo, ST and AT, contributed to the design of the study and writing of the final manuscript.

Funding The study is funded by Barts Charity (funder reference MGU0371). Additionally, Barkey Plasmatherm provided thawers to support the trial. Barts Charity have reviewed the funding application, and will have oversight of study progress, but neither of the funders have any role in the collection, analysis, and interpretation of data and in writing the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Laura Green http://orcid.org/0000-0003-4063-9768
Jahnavi Daru http://orcid.org/0000-0001-5816-2609
Julie Dodds http://orcid.org/0000-0002-6041-1456
Francisco Jose Gonzalez Carreras http://orcid.org/0000-0002-3043-7495
Doris Lanz http://orcid.org/0000-0001-9879-3069
Javier Zamora http://orcid.org/0000-0003-4901-588X
Maria del Carmen Pardo Llorente http://orcid.org/0000-0002-4623-6321
Teresa Pérez Pérez http://orcid.org/0000-0003-0439-8952
Lorna Sweeney http://orcid.org/0000-0002-1630-467X
Shakila Thangaratinam http://orcid.org/0000-0002-4254-460X
Khalid Saeed Khan http://orcid.org/0000-0001-5084-7312

REFERENCES

1 Khan KS, Wojdyla D, Say L, *et al*. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–74.
2 Knight M, Callaghan WM, Berg C, *et al*. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International postpartum hemorrhage Collaborative group. *BMC Pregnancy Childbirth* 2009;9:55.
3 Scotland HI. Scottish Confidential audit of severe maternal morbidity: reducing avoidable harm. 10th annual report.. Available: http://www healthcareimprovementscotland org/our_work/reproductive,_maternal_child/programme_resources/scasmm aspx [Accessed 29 Jan 2016].
4 Wise A, Clark V. Strategies to manage major obstetric haemorrhage. *Curr Opin Anaesthesiol* 2008;21:281–7.
5 Gayat E, Resche-Rigon M, Morel O, *et al*. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. *Intensive Care Med* 2011;37:1816–25.
6 Charbit B, Mandelbrot L, Samain E, *et al*. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007;5:266–73.
7 Cortet M, Deneux-Tharaux C, Dupont C, *et al*. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth* 2012;108:aes096:984–9.
8 Green L, Knight M, Seeney F, *et al*. The haematological features and transfusion management of women who required massive transfusion for major obstetric haemorrhage in the UK: a population based study. *Br J Haematol* 2016;172:616–24.
9 Holcomb JB, Tilley BC, Baraniuk S, *et al*. 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* 2015;313:471–82.
10 Shakur H, Roberts I, *et al*, 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;376:23-–32.
11 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (woman): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:2105–16.
12 Mavrides E, Allard S, Chandraharan E, *et al*. Prevention and management of postpartum haemorrhage. *BJOG* 2016.
13 Hunt BJ, Allard S, Keeling D, *et al*. A practical guideline for the haematological management of major haemorrhage. *Br J Haematol* 2015;170:788–803.
14 Prevention and management of postpartum haemorrhage: Green-top guideline No. 52. *BJOG* 2017;124:e106–49.
15 Bateman BT, Berman MF, Riley LE, *et al*. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg* 2010;110:1368–73.
16 Eldridge S, Kerry S. *A practical guide to cluster randomised trials in health services research*. Chichester, UK: Wiley, 2012.
17 Moss N, Daru J, Lanz D, *et al*. Involving pregnant women, mothers and members of the public to improve the quality of women's health research. *BJOG* 2017;124:362–5.
18 Zaidi A, Kohli R, Daru J, *et al*. Early use of fibrinogen replacement therapy in postpartum Hemorrhage-A systematic review. *Transfus Med Rev* 2020:j.tmrv.2019.12.002.