Clinical and cost-effectiveness of a maternity quality improvement programme to reduce excess bleeding and need for transfusion after childbirth: the Obstetric Bleeding Study UK (OBS UK) Stepped Wedge Cluster Randomised Trial

PROTOCOL V3.0

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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General Information This protocol describes the "Clinical and cost-effectiveness of a maternity quality improvement programme to reduce excess bleeding and need for transfusion after childbirth: the Obstetric Bleeding Study UK (OBS UK) Stepped Wedge Cluster Randomised Trial", and provides information about the procedures for entering maternity units into the trial and individual participants into sub-studies. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to the Cardiff Trials Unit.

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Trial Co-ordination:

The OBS UK trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the OBS UK Trial Management Group (TMG).

For **all queries** please contact the OBS UK team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

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Serious Adverse Events:

SAE reporting

As the components of the care bundle being tested are recommended and used throughout the UK, there are no adverse events which would be anticipated as a unique consequence of participation in the trial. Therefore, no expedited reporting of adverse events is in place. (See section 13 for more details).

Contents

Glossary of abbreviations

AE	Adverse Event
AOC	Acute Obstetric Coagulopathy
APTT	Activated partial thromboplastin time
CCF	Citrated Functional Fibrinogen
CFIR	Consolidation Framework for Implementation Research
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DSCHR	Division for Social care and Health Research
EDI	Equality, diversity and inclusion
eDRIS	Electronic Data Research and Innovation Service
FFP	Fresh frozen plasma
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GP	General Practitioner
HAREF	Health and Race Equality Forum
HB	Health Board
HE	Health Economics
HEE	Health Education England
HES	Hospital Episode Statistics
HRA	Health research Authority
IC	Informed consent
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Maximum amplitude

MDT	Multi-disciplinary team
MESH	Message Exchange for Social Care and Health
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPT	Normalisation Process Theory
NSH	National Safe Haven
OBS	Obstetric Bleeding Strategy
OBS UK	Obstetric Bleeding Study UK
PBPP	Public Benefit and Privacy Panel for Health
PDSA	Plan-do-study-act
PHS	Public Health Scotland
PI	Principal Investigator
PIS	Participant Information Sheet
PPH	Postpartum haemorrhage
PT	Prothrombin time
PTSD	Post-traumatic stress disorder
QA	Quality Assurance
QBL	Quantification of blood loss
QC	Quality control
QI	Quality improvement
QL (QoL)	Quality of Life
R&D	Research and Development
RBC	Red Blood Cell
RCOG	Royal College of Obstetrics and Gynaecology
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROTEM	Rotational Thromboelastometry
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TEG	Thromoelastography

TMF	Trial Master File
TMG	Trial Management Group
TRE	Trusted Research Environment
TSC	Trial Steering Committee
USM	Urgent safety measures
VHA	Viscoelastometric haemostatic assays

Definitions

A **maternity unit** is defined as including all women giving birth in a consultant-led obstetric unit, midwifery-led unit, at home, or elsewhere within that service.

The terms **woman/women/mother/breast feeding** are used consistently throughout this document pertaining to the primary person receiving care and giving birth. We acknowledge that not all birthing people use these terms and we want to promote gender equality throughout to ensure respect for the unique psychological, physiological, and social needs of each individual. We specifically acknowledge the trans and non-binary experience of pregnancy and PPH and will ensure to engage with people with this experience in a respectful, safe, and inclusive way.

Exclusive breast feeding is defined as breast milk only and no formula milk.

The **birth partner (BP)** is the person who was present at the time of the birth and PPH, supporting the woman. The **economic partner (EP)** is defined as the person who lives or contributes financially with the woman who has given birth and this may be the birth partner (BP), a spouse, a relative such as a parent or other individual.

Postpartum haemorrhage (PPH) describes bleeding during and after childbirth.

Maternities is all women and birthing people who give birth (including live and stillbirth) in maternity services.

Births is all registerable births (any baby born live (at any gestation) or a stillbirth/termination of pregnancy if this occurs after 24 weeks of gestation).

1. Amendment History

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

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
Response to initial ethics submission	1.1	21.08.2023	Removal of GP letter for sub studies
	1.2		1. Updated with REC reference. 2. Updated with ISRCTN number 3. Change for Will Parry-Smith from Shrewsbury and Telford to Keele University. 4. Update to breast feeding questionnaire 5. Update to opt out strategy 6. Correction of typo 7. Data flow diagram 8. Correction to add in recorded consent to process evaluation summary 9. Addition of sickle cell disease 10. Change to data collection in Northern Ireland 11. Definitions of births and maternities.
	1.3		1. Removal of Catherine Pope as co-applicant. 2. Addition of Lisa Hinton as co-applicant.

			3. Addition of Linda Adara as Trial Manager, removal of Laura Johnson as Administrator, addition of Christopher Lloyd as Administrator. Removal of Dimitrios Profer as Trial Statistician, replaced by Philip Pallman. 4. Addition of methods of consenting to the psychology and health economic sub studies and wording around consecutive consent. 5. Addition of automated text reminders to consenting psychology and health economics sub studies. 6. Change of logo following PPI input. 7. Inclusive wording added to lay summary to include women and birthing people. 8. Inclusion of monitoring of aggregate data. 9. Regional consenting clarification on collecting aggregate data (Northern Ireland).
	1.4		1. Update version No. and date to V1.4 26.04.2024 2. Update to trial manager staff. Removal of Sarah Kotecha & Linda Adara, replaced with Rachel Deere 3. Section 9.4 Informed consent – Psychological/cost-effectiveness sub-studies updated:

			a. Clarified process for taking online consent. b. Addition of offer of £15 voucher as a thank you 4. Section 12.2 Psychological sub-study: added in wording to clarify sending of automatic text reminders where possible. 5. Update to figure 2 to reflect condensed data collected for psychology and health economics sub studies.
	1.5	04.07.2024	1. Statistics update post TSC discussion 2. Changes to the way information is provided to women in Scottish sites following PBPP approval 3. Changes to wording in section 13 4. Web address for forms added
	1.6	09.07.2024	1. A researcher will be taking photographs for the process evaluation work (of objects not of people or personal data). 2. Minor changes to process evaluation participant numbers 3. Changes made to wording in section 13 in protocol 1.5 reverted back to wording in protocol version 1.4
	2.0	06.08.2024	1. Sub-study on empiric vs. targeted data added (OBS E-Fib) 2. Sub-study on mechanisms added (OBS M-Fib)

			3. Alteration in the ROTEM devices therefore the diagnostic threshold which was previously 12mm has changed to 9mm
	2.1	15.10.2024	1. Wording change related to adverse drug reactions 2. added in additional audit and case note review during the first month of OBS UK care (after implementation) 3. clarified that questionnaire follow-up in the psychological and economic sub-study will continue for 2 weeks only. 4. Clarified that in NI routine data will be collected but not individually identified 5. Sites in any sequence of the stepped wedge study may participate in the OBS E-Fib sub-study (not just some sequences).
	2.2	02.12.2024	1. Number of maternity units involved in e-fib removed (open to as many units as possible) 2. Additional blood sample taken 1 hour post delivery in m-fib for healthy controls. 3. Eligibility for E-fib can be identified retrospectively
	2.3	11.12.2024	Sub-studies sample size amended
	2.4	12.02.2025	1. Trial team details updated. 2. Figure 2 updated: 1. Amended participant n to n=40; 2. Removed reference to seq 2-5 in

			under Psych and HE questionnaires; 3. Addition of sequence under Standard PPH care and OBS UK care. 3. Correction to figure 4: replaced ≤ with < 4. Section 8.1: Clarification of inclusion of partners also for the psychological and health economic study. 5. Section 9.4, Psychological & Health economic sub study: 1. Increased value of thank you voucher for PPH sample; 2. Clarified reminder will be by text and letter or phone 6. Figure 5: Updated participant number from n=23 to n=40 in line with previous sample size change. 7. Section 12.3 Cost effectiveness study: Clarification on recruitment of non PPH participants from any site. 8. Section 5.3 correction to wording of primary outcome measure. 9. Section 14.3 Sample size, Psychological and cost effectiveness sub-study: slight correction of grammar.
	3.0	05/03/2025	1. Amendment of study team members details from Gwen Moody to Claire Potter. 2. Amendment of acronyms list to include amended trusted research environment. 3. Addition of mental health study throughout document (synopsis, 5.2 secondary objectives, 5.4 secondary outcome

			measures, 8.1 inclusion criteria, 8.2 Exclusion criteria, 9.1 Participant identification, 9.4 informed consent, 10.2 loss to follow-up, 12.3 trial procedures, 14.3 sample size). 4. Section 8.1 inclusion criteria cost effectiveness sub study: re-inserted '500ml' as the limit for inclusion non PPH participants as this was deleted in error during the last amendment. 5. Section 8.1 inclusion criteria E-fib: clarification that coagulation results to be included can be up to 120 minutes before coagulation blood product transfusion and 60 minutes after. 6. Section 5.4: Figure 4 amended wording to clarify process. Table formatted. 7. Slight amendment to clarify wording in 10.1 withdrawal process regarding consent for future contact. Also correction to withdrawal from M-fib to bring in alignment with consent form. 8. Section 10.2 Lost to follow-up: Amended follow-up window in Psychological/cost effectiveness sub studies to be in line with previous amendment for 6 week and 6 months questionnaires to 6 weeks + 4 weeks and 6 months + 8 weeks. 9. Section 5.4 Secondary outcomes: same correction as above to follow-up window for

			6 weeks + 4 weeks in the psychological/cost effectiveness sub studies. 10. Section 12.3 Trial procedures - Mental Health study: Addition of this section to outline the procedures of the mental health study. 11. Tabel 1 updated to include timeline for the mental health study. 12. Section 14.3 Sample size – Psychological and cost effectiveness sub study correction to the sample size in some places, to make sure consistent throughout. 13. Section 14.3 – Sample size, addition of sample size for the mental health study. 14. Section 16.1.2 Targeted source data and routine NHS sources: Amendment to the trusted research environment from SAIL databank in Wales to the Scottish National Safe Haven (NSH) in University of Edinburgh, operated by EPCC. 15. 16. Section 16.1.3 Target source data & section 16.2 Linkage of target source data with national datasets: correction to reference of trusted research environment being used.Figure 8 & figure 9: Amendment to nation specific data flow diagrams to indicate change of TRE. 17. Section 16.3 Paper CRFs: correction of wording regarding use of paper CRFs or telephone.

			18. 16.3.2 Electronic CRF – Data protection: amendment of acronym of trusted research environment used.

2. Synopsis

Short title	Obstetric Bleeding Study UK
Acronym	OBS UK
Funder and ref.	NIHR 152057
Trial design	Stepped wedge cluster randomised trial
Trial participants	All women giving birth at, or in the care of, participating maternity units will be included. The maternity unit is the unit of randomisation
Planned sample size	36 maternity units, corresponding to approximately 189,000 women
Inclusion criteria (sites)	• Maternity unit with >2000 births per year • Local NHS maternity leaders support the implementation of the OBS UK intervention and quality improvement (QI) time for the local champion team. This must include protected midwifery time (4 hours/week) and non-clinical time for consultant obstetrician, anaesthetist, and haematologist from supporting professional activity during the 9-month implementation period
Exclusion criteria	• Maternity units that have adopted the entire OBS UK obstetric haemorrhage care bundle • Maternity units that use viscoelastic point-of-care tests of haemostasis on the consultant-led delivery suite or in obstetric theatres • One Trust/ Board may contain several maternity units, if this is the case only one maternity unit per Trust/Board can be included in the study and other maternity units from that Trust/Board are excluded
Control period	Standard UK postpartum haemorrhage (PPH) care as delivered in each maternity unit prior to implementation of the intervention
Implementation period	The Obstetric Bleeding Strategy PPH care bundle introduced using QI methods over 9 months

Intervention	The Obstetric Bleeding Strategy PPH care bundle: • Assessment of every woman's bleeding risk • Quantification of blood loss for all women from the time of birth • Escalation of multi-professional care to more senior staff at defined volumes of blood loss with appropriate medical intervention • At 1 L blood loss with ongoing bleeding, or earlier for clinical concern, a point-of-care test of haemostasis should be performed and the OBS UK blood component infusion algorithm followed
Intervention period	OBS UK PPH care as delivered in each maternity unit following completion of the 9-month implementation period
Duration	• The control (standard care) and intervention maternity unit level outcome data will be collected over periods of between 3 and 18 months (variation in length of follow up is due to the stepped wedge design) • Individual women will be followed up for up to 6 months after birth in psychology and cost effectiveness sub-studies
Planned trial period	45 months
Primary objective	To test the effectiveness of the Obstetric Bleeding Strategy intervention compared to standard care on clinical and psychological PPH outcomes after childbirth and to evaluate the cost-effectiveness of the OBS intervention compared to standard care
Secondary objectives	To conduct a process evaluation of the Obstetric Bleeding Strategy intervention. To conduct a prospective observational sub-study investigating coagulopathy in obstetric haemorrhage. This will consist of part 1, investigation into empiric vs. targeted blood coagulation product transfusion for the treatment of acquired fibrinogen deficiency in obstetric haemorrhage (the OBS E-Fib sub-study) and part 2, investigation into the mechanisms of obstetric coagulopathy through

collection and storage of plasma samples for future central laboratory analysis (the OBS M-Fib sub-study).

Primary outcomes

The proportion of women receiving allogenic red blood cell transfusion for PPH

Secondary outcomes

Clinical outcomes: Blood loss volume, hysterectomy, maternal death, transfer to a higher level of care (Level 2,3), cardiovascular shock, organ dysfunction, need for blood components (allogenic and autologous red cells, plasma, platelets, concentrated fibrinogen sources), coagulopathy, haemostatic surgical and radiological interventions (uterine tamponade balloon insertion, uterine brace suture, return to theatre, interventional radiology), length of hospital stay, breastfeeding (timing and type of first feed initiated, maintenance, exclusivity at 6 weeks), neonatal death and stillbirth

Psychology sub-study: Woman and their birth partner's postnatal mental health (post-traumatic stress and postnatal depression symptoms), acceptability of and satisfaction with intervention, breastfeeding and adverse effects of intervention on mother, partner (and baby)

Mental health sub study: A qualitative evaluation of women's and birth partners' experiences of care in a subsample of the psychology sub-study participants with and without post-traumatic stress symptoms.

Health Economic sub-study: Cost-effectiveness expressed as incremental cost per confirmed case of red blood cell transfusion avoided and incremental cost per quality adjusted life year gained over a lifetime horizon

Process evaluation: A mixed-method approach to understand implementation of the care bundle using QI methodology during the pilot study in Wales (retrospective review) and during the OBSUK trial, exploring how the intervention was deployed and possible improvements to inform wider implementation

OBS E-Fib: To compare the proportion of women with fibrinogen levels $\leq$2g/L who achieve levels >2g/L after the first cycle of blood coagulation product

	transfusion between empirical blood coagulation product (standard, usual UK treatment) and concentrated fibrinogen transfusion (OBS UK treatment). **OBS M-Fib**: **Mechanistic study:** Double-spun plasma samples will be collected and stored at local sites for subsequent testing in central laboratories to improve understanding of the mechanisms underlying coagulopathies associated with PPH.
Additional descriptors	Ethnicity, Index of Multiple Deprivation, Body Mass Index (BMI), age, spontaneous (unassisted) vaginal birth, assisted vaginal birth, planned and unplanned caesarean birth, induction of labour and cause of PPH
Consent	• Individual written consent for participation will not be sought for aggregate data. • In England, routinely collected data retrieved from NHS databases will be linked to data provided by the sites for women who have a PPH of >1.5L and/or receive a blood transfusion for PPH (including those who take part in the E-Fib study). Women who have opted out of national digital data use or use of their data for the OBS UK study alone will not be included in the routine data collection or linkage. • In Scotland, anonymised data will be provided by the sites for women who have a PPH of >1.5L and/or receive a blood transfusion for PPH. The only personal data collected will be the date of birth of the baby. Routinely collected data retrieved from NHS databases will be linked to data provided by the sites for women who have a PPH of >1.5L and/or receive a blood transfusion for PPH. This will be facilitated by sites maintaining a spreadsheet of Study IDs and the corresponding CHI number, which will be provided to NHS Scotland at the time of the linkage. There is no option to for national opt-out in Scotland. • In Northern Ireland, pseudonymised data will be provided by the sites for women who have a PPH of >1.5L and/or receive a blood transfusion

for PPH. This will not be linked to NHS databases and consent will not be sought.

- Individual written, telephone or electronic informed consent will be obtained for the psychology, mental health, economic and process evaluation questionnaires, surveys and interviews and OBS M-Fib.

3. Trial summary & schema

3.1 Trial schema

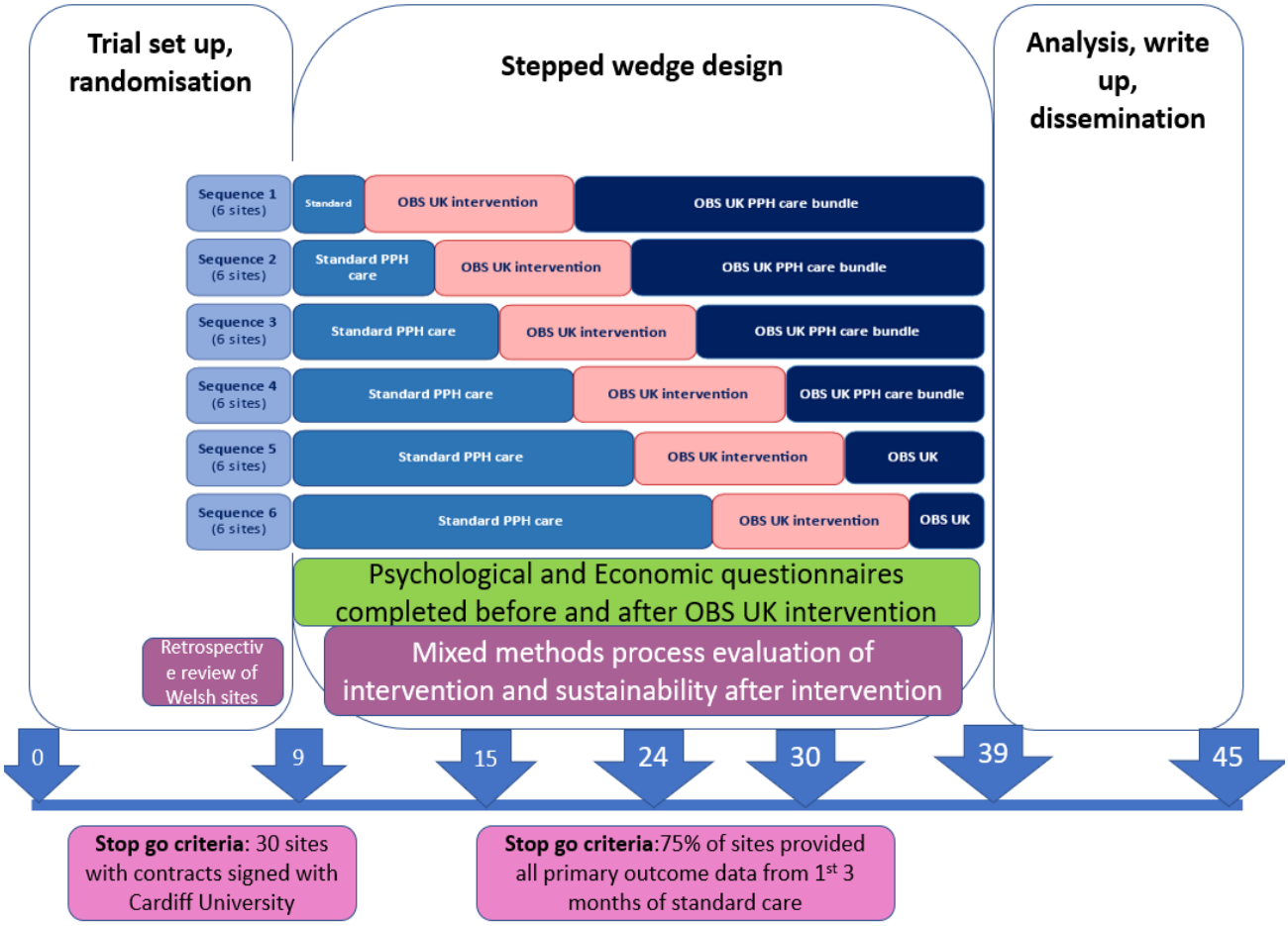


Figure 1. Trial timeline

3.2 Trial lay summary

Excess bleeding is the most common complication of childbirth. Every year about 50,000 women and birthing people in the UK lose 1 litre (almost 2 pints) of blood or more. Many need a blood transfusion or are admitted to intensive care and find the experience of bleeding traumatic, developing mental health issues after having their baby. Minority ethnic backgrounds are disproportionately affected.

We developed a care bundle for treating bleeding during childbirth in Wales called the 'Obstetric Bleeding Strategy'. The care bundle is: 1) Assessment of every patient's bleeding risk, 2) Real-time

measurement of blood loss after all births, 3) A consistent approach to managing excess bleeding and involving more senior clinicians, 4) Bedside tests to rapidly identify and treat abnormal blood clotting. This contrasts with current UK guidelines which recommend measuring blood loss only after excess bleeding is identified.

This national study follows on from our pilot study in which we found that the Obstetric Bleeding Strategy care bundle could be successfully adopted by maternity units. The results from this pilot were encouraging, but since this was a small study with limited data, we do not know whether the improvements seen were due to the change in care, or whether the care bundle is value for money. To find this out, this study will compare clinical outcomes, psychological wellbeing and cost of care for women and birthing people in maternity units that use the care bundle with patients receiving standard care.

We will use routine NHS data on about 189,000 women from 36 NHS maternity units over 30 months. We will also collect data about ethnicity and socioeconomic groups to see whether outcomes are affected by these variables. All data will be collected from women and birthing people whether they have excess bleeding or not. All maternity units will start with a period of standard care, they will then adopt the Obstetric Bleeding Strategy care bundle over 9 months, followed by a period of Obstetric Bleeding Strategy care. To measure how effective the Obstetric Bleeding Strategy care bundle is, we will compare rates of blood transfusion before and after it is introduced. We will also study intensive care admission, hysterectomy, breastfeeding rates and various other outcomes.

Women and birthing people with experience of excess bleeding have advised us on the study's importance, its design, and outcomes. Add-on studies will look at the effect of the Obstetric Bleeding Strategy care bundle on the psychological wellbeing of women, birthing people and birth partners and how units adopt the care bundle, with special attention to ethnicity and organisational factors. This will include interviewing women, birthing people, their birth partners and staff to understand their experiences of excess bleeding and whether the Obstetric Bleeding Strategy care bundle changes how teams deliver care. The cost of implementing the bundle and financial impact of having excess bleeding will also be studied. In some sites, blood samples will be stored for future testing to improve our understanding of blood clotting problems after childbirth.

This research will establish whether (and how) the Obstetric Bleeding Strategy care bundle improves outcomes and experiences of people giving birth. We will share our findings widely with the support of UK maternity providers and patient representatives.

4. Background

The clinical problem

Globally, bleeding during and after childbirth (postpartum haemorrhage, PPH) is the leading cause of maternal death.[1] There has been no improvement in maternal death due to PPH in the UK over the last 15 years despite a modern healthcare system and comprehensive Royal College of Obstetrics and Gynaecology (RCOG) guidelines. [2, 3] PPH is a common complication of childbirth, causing 80% of severe maternal morbidity. [4] In the UK about 50,000 women per year have severe PPH (>1L) with 28% of these requiring red blood cell (RBC) transfusion. [2, 3, 5] The incidence of PPH in many countries is increasing as risk factors become more common. [6-9] About 5000 women per year in the UK have massive PPH (>2.5L), with about 320 requiring a hysterectomy and 350 being admitted to the intensive care unit (ICU) and therefore being separated from their baby as well as suffering severe morbidity. [4, 10, 11] PPH has long term psychological consequences for women and their birth partners including post-traumatic stress disorder (PTSD) in 5-45% of cases and impaired infant bonding. [12-17] Significant inequalities in materno-fetal outcomes based on multiple intersectional disadvantages such as non-white ethnicity and socioeconomic deprivation have been identified in the UK. [2]

Initiatives to improve PPH-related maternal outcomes usually focus on a single intervention such as drugs to induce uterine contraction. [5] However, it is likely that only a standardised, integrated approach will address all problems in care. This includes timely escalation of care to senior clinicians so that they can identify the cause of the PPH and institute appropriate pharmacological and surgical interventions with resuscitation including coagulation products specific to the woman's needs. [18-23] Effective monitoring systems and an open culture of sustained individual, team and institutional learning are required. [24] National reviews highlight the need to improve and standardise maternity care across the UK, with recent reports finding wide variations in practice and deficiencies in management in 80% of massive PPH cases. [2, 25-27]

Obstetric Bleeding Strategy (OBS) PPH care bundle

Informed by research, a PPH care bundle was developed by multi-professional maternity service stakeholders and was called the Obstetric Bleeding Strategy (OBS, or locally in Wales OBS Cymru). The PPH care bundle was successfully implemented in all 12 obstetric units in Wales between 2017-2018 in an observational pilot study (OBS for Wales/OBS Cymru). [22, 28] OBS consists of four interdependent components (see Figure 6, Section 11.1.1).

Evidence for the OBS PPH care bundle

Measuring blood loss from delivery after all births: Visual estimation of blood loss is inaccurate. [29] We have shown that real time, accurate and cumulative quantification of blood loss (QBL) at all births from the time of delivery using validated gravimetric and volumetric techniques is reproducible and feasible. [30] When incorporated into a care bundle, QBL can standardise communication, improve timely escalation of care and bring interventions earlier so that bleeding is stopped more quickly in the majority of cases. [31]

Patient specific coagulation product resuscitation: Fibrinogen is a key component of a blood clot and falls to critically low levels before other clotting factors during PPH. [32] Low fibrinogen is associated with specific obstetric conditions such as placental abruption but may also occur unexpectedly. [33] Basing coagulation product replacement on the cause and/or volume of PPH is inappropriate in the majority of cases [11, 33].

The OBS approach incorporates point-of-care (bedside) measurement of fibrinogen levels and overall coagulation so that clotting results are available in minutes, compared to laboratory results which take over 1h. This allows early identification and correction of low fibrinogen levels with concentrated fibrinogen products infused at a time and dose specific to the patient. [34] Fibrinogen concentrate corrects fibrinogen levels rapidly and can be prepared in 5-10 minutes.

In a double-blind RCT, OBS2, we showed that a fibrinogen level of >2g/L was adequate for clotting during PPH and a pre-specified subgroup analysis of women with fibrinogen <2g/L found that those treated with fibrinogen concentrate received fewer blood products and had smaller bleeds compared to placebo. [35, 36] We have validated algorithms for two point-of-care device, ROTEM and TEG to identify low fibrinogen levels during PPH. [37, 38]

The use of Quality improvement (QI) to improve obstetric care

The need to improve the quality of obstetric care and reduce variation has been highlighted in multiple recent UK reports. Challenges identified include availability of reliable outcome data, staff pressures, varied size and geography of obstetric units and financial constraints.

QI methods provide a means of introducing interventions into healthcare systems and all obstetric units are expected to have a rolling QI programme. Publication of guidelines and or protocols alone does not automatically lead to adoption and QI methods are therefore advocated as a means of achieving a change in practice. [49, 50]

Empiric vs. targeted fibrinogen replacement (OBS E-Fib) and Mechanisms (OBS M-Fib) sub-studies (further background in Appendix 1).

The OBS E-Fib sub-study will investigate empiric vs. targeted fibrinogen replacement for the treatment of acquired fibrinogen deficiency in obstetric haemorrhage. We will collecting data on the level of Clauss fibrinogen in patients who have a coagulopathy (defined as Clauss fibrinogen <2 g/L), before and after infusion of coagulation blood products.

The OBS M-Fib sub-study will investigate mechanisms of obstetric coagulopathy. In selected OBS UK sites, collection and storage of double-spun plasma samples will occur locally for subsequent analysis in central laboratories. Clinical data of the woman or birthing person and their baby(s) will be collected to be analysed in association with the blood results.

These sub-studies will provide, robust evidence regarding the nature, incidence, diagnosis and optimal management of coagulopathy in PPH, which is crucial in improving maternal outcomes. Linking the sub-studies to the OBS UK Trial is an efficient way of performing research, whilst providing a mechanistic interpretation of the OBS UK results.

4.1 Rationale for current trial

There is currently a lack of a standardised approach to PPH in the UK.[39] The OBS UK study will compare the OBS PPH care bundle introduced using QI methods over a 9-month period with standard NHS care. The intervention has been associated with improved outcomes for PPH in a pilot study in Wales but needs to be compared to standard NHS UK care in a rigorous clinical study to test

whether the OBS UK care bundle will successfully transfer outside Wales. The demographic and socio-economic characteristics of the UK sites will also allow the wider issues of equality, diversity and inclusion (EDI) to be considered, which was not possible in the pilot study. The selection of 36 sites across the UK will therefore include areas with significant deprivation and ethnically diverse populations.

The study will align with several of the Immediate and Essential Actions to improve care and safety in maternity services across England recommended by the Ockenden report [39] including escalation and accountability, multidisciplinary training, obstetric anaesthesia and support for families. The study will incorporate an implementation analysis to inform optimal adoption and mechanisms of impact, ensuring that changes are fully evaluated and learning can be applied to other healthcare settings.

There is a lack of evidence to guide the treatment of low fibrinogen levels during obstetric bleeding and a sub-study will investigate the efficacy of different options to help inform future clinical guidelines. The mechanisms underlying haemostatic impairment during PPH are poorly described. To address this, blood samples will be collected during the OBS UK care period of the study at some sites for future analysis at central laboratories. These data will help to guide clinical management of haemostatic impairment during PPH.

5. Trial objectives/endpoints and outcome measures

5.1 Primary objectives

To test the effectiveness of the Obstetric Bleeding Strategy (OBS) intervention compared to standard care on clinical and psychological obstetric bleeding outcomes after childbirth and to evaluate the cost-effectiveness of the OBS intervention compared to standard care.

5.2 Secondary objectives

To conduct a mixed methods process evaluation of the OBS intervention, prospectively in participating UK sites, and retrospectively in four units in Wales that adopted the OBS intervention during the pilot study. To conduct a process evaluation of the Obstetric Bleeding Strategy intervention. To conduct an in depth qualitative evaluation of women and birth partners with and

without PTSD symptoms who experienced a PPH. To conduct a prospective observational sub-study on empiric vs. targeted fibrinogen replacement for the treatment of acquired fibrinogen deficiency in obstetric haemorrhage (OBS E-Fib sub-study) and collect plasma samples to investigate the mechanisms underlying obstetric coagulopathy (M-Fib sub-study).

5.3 Primary outcomes measure

The primary outcome will be the proportion of women who receive an allogenic red blood cell (RBC) transfusion for PPH which will be compared between the standard care period and the OBS UK care period. Any RBC transfusion administered for obstetric bleeding within 4 hours before birth up until hospital discharge will be included. If there is uncertainty about the main indication for a RBC transfusion, the local principal investigator will decide whether a transfusion was given for obstetric bleeding or not. Only data collected from months 5 to 9 of the 9-month implementation period will contribute to the primary outcome. Further details regarding data collection are outlined in Section 12 and Figure 2.

5.4 Secondary outcomes measures

Clinical outcomes

1. **Blood loss**: Total blood loss volume within 4 hours prior to and 24 hours after birth
2. **Hysterectomy**: Number of women undergoing hysterectomy due to PPH
3. **Maternal death:** Number of women who died following PPH
4. **Higher level of care:** Number of women transferred to higher level of care (Level2/3) outside of the obstetric unit for complications following PPH
5. **Cardiovascular shock**: Number of women transferred to higher level of care outside of the obstetric unit for vasopressor infusion following PPH
6. **Organ dysfunction**: Number of women transferred to higher level of care outside of the obstetric unit for organ support following PPH
7. **Blood transfusion:** Number of women transfused cell salvage red blood cells and the volume within 4 hours before birth up until discharge for obstetric bleeding
8. **Other blood components/products transfused:** Number of women transfused coagulation products including type of product (FFP, cryoprecipitate, platelets or fibrinogen concentrate) and number of units within 4 hours before birth up until discharge for obstetric bleeding

9. **Coagulopathy:** Number of women with fibrinogen levels ≤2g/L, ROTEM Fibtem A5 <9mm or TEG CFF MA (by 10 minutes) ≤17mm, PT/APTT >1.5x midpoint of normal reference range and platelet count <75 $x10^9$ within 4 hours prior to and 24 hours after birth
10. **Haemostatic surgical and radiological interventions:** Number of women requiring uterine tamponade balloon insertion, uterine brace suture, transfer to theatre or any radiological intervention for PPH
11. **Neonatal death and stillbirth rate:** Number of neonatal deaths and stillbirths
12. **Length of hospital stay:** Time from birth until mother's discharge
13. **Breastfeeding:** First feed timing, type, maintenance of breastfeeding including breast milk only at 6 weeks
14. **Women and birth partner's postnatal mental health, women and birth partner's acceptability of and satisfaction with intervention, breastfeeding and adverse effects of intervention on mother, baby and birth partner:** Psychological quantitative study (described below).

Additional descriptors

Descriptors will be collected and compared between women with and without PPH including: ethnicity, sickle cell descriptors, socioeconomic group, body mass index, age, mode of birth, place of birth, parity, induction of labour, cause of PPH.

Psychology outcomes

The outcomes for the psychology sub-study will be collected via questionnaires at 6 weeks (±4 week) and 6 months (±8 weeks) after birth (see also Section 12 and Figure 2):

1. **Symptoms of depression** (mother and birth partner): measured on the Edinburgh Postnatal Depression Score [40]
2. **Symptoms of post-traumatic stress disorder** (mother and birth partner): measured on the Impact of Events Scale Revised with PPH as a specific event
3. **Mother and baby bonding:** Mothers' Object Relations Scale [41]
4. **Perspective on whether PPH was psychologically traumatic** (mother and birth partner): Diagnostic and Statistical Manual V criterion via a specific criterion question: "You felt you/your birth partner were at risk of death or serious harm", yes/no

5. **Interpersonal factors associated with the experience of childbirth** (mother and birth partner): Semantic differential questions co-produced with the study's patient public involvement group, to capture what was important to them, and their birth partners at the time of their PPH (6 weeks only)
6. **Initiation and maintenance of partial/exclusive breastfeeding** (mother)
7. **Access to professional support or intervention for psychological symptoms related to the birth experience. What, if any, support has been accessed and participant views on this.** (mother and birth partner, 6 months only)

Mental health outcomes

The outcomes for the mental health sub-study will be collected qualitatively from women and birthing partners who experienced a PPH and include:

1. Whether or how experiences of care relate to subsequence levels of post-traumatic stress symptoms at 6 months.

Cost-effectiveness outcomes

The outcomes for the cost-effectiveness analysis (including EQ 5D5L) will be collected via questionnaires at 6 weeks (±4 week) and 6 months (±8 weeks) after birth (see also Section 12 and Figure 2):

1. **Incremental cost per confirmed case of allogenic red blood cell transfusion avoided**
2. **Incremental cost per quality-adjusted life year gained over a lifetime horizon**

Process evaluation outcomes

The outcomes for process evaluation are further described in Section 12 and Figure 2 and will be:

1. **Prospective data from all sites**
    a. **Surveys**

    Site context survey at study start and online staff survey at end of the 9-month implementation period

    b. **QI measures**

        i. Monthly run charts of PPH volume and RBC transfusion (run charts are displays of time-series data shown in graph form), throughout the implementation and OBS UK periods

ii. Audit and case notes review during implementation (1, 4 and 7 months)

c. **Assessment of sustainability and or decay of components** of OBS UK care bundle

i. Audit and case notes review in the first month after the end of the 9 month implementation period and at the end of study

d. **Targeted source data**

Failure to detect a difference between standard and OBS UK care may be due to changes in clinical care which impact on the primary outcome (eg. management of antenatal anaemia and timing of clinical escalation). Therefore haemoglobin and coagulation tests and time of clinical escalation will be collected as process measures for women who experience PPH >1.5L and or receive a blood transfusion due to obstetric bleeding, see section 12.4.

2. **Case studies**

Prospective ethnographic and qualitative data collection from six sites (one per sequence) during standard care, implementation and OBS UK care periods and ethnographic and qualitative data collection in four maternity units in Wales where the intervention is embedded into standard care.

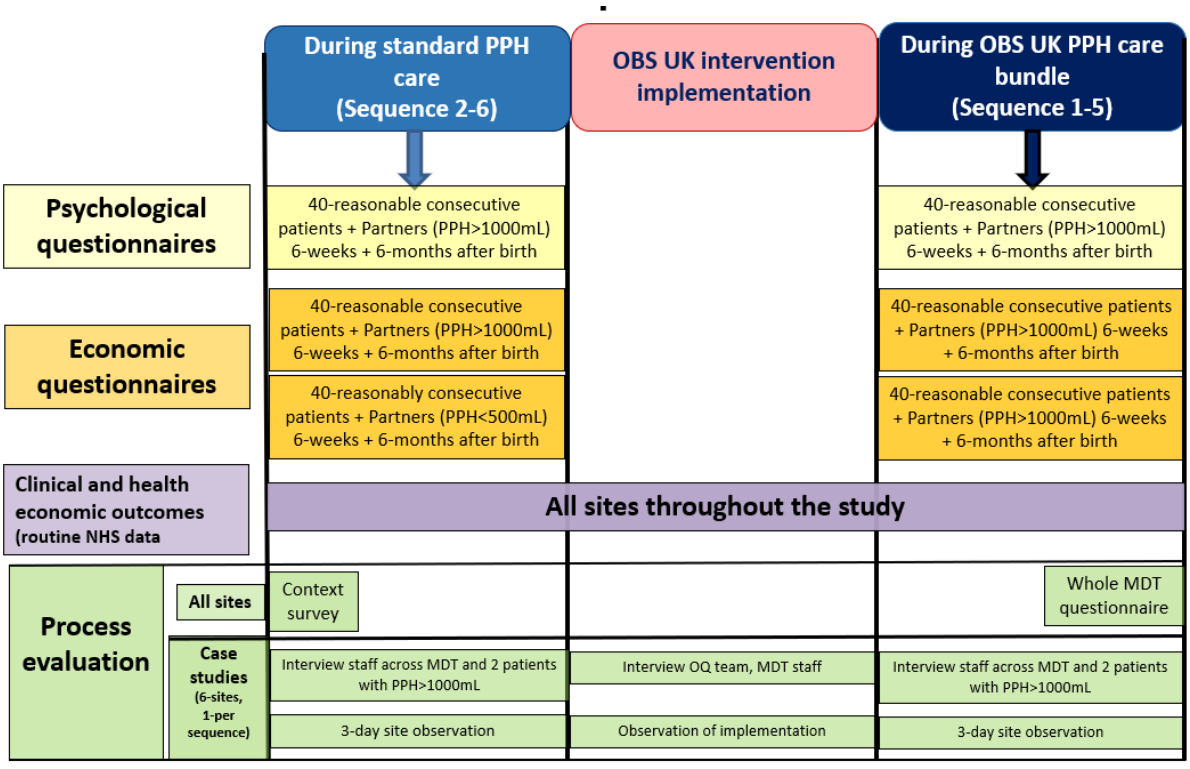


Figure 2. Data collection for clinical outcomes, psychological and economic sub-studies and process evaluation.

Four maternity units that took part in the OBS Cymru study will have site visits from the national process evaluation team. These visits will be performed before the 30 month stepped wedge OBS UK study starts. The outcome of this work does not affect starting the OBS UK trial. The **birth partner (BP)** is the person who was present at the time of the birth and PPH, supporting the woman. The **economic partner (EP)** is defined as the person who lives or contributes financially with the woman who has given birth and this may be the birth partner (BP), a spouse, a relative such as a parent or other individual.

OBS E-Fib outcomes

Comparison of empirical blood coagulation product transfusion (standard, usual UK treatment) versus point of care guided concentrated fibrinogen transfusion (OBS UK treatment) in treatment of acquired hypofibrinogenaemia (≤2g/L) to achieve fibrinogen levels >2g/L during PPH resuscitation will be undertaken. A summary of data collection is illustrated in Figure 3 and further described in section 12.5.

OBS M-Fib outcomes

Double-spun plasma samples will be collected and stored to investigate the mechanisms, incidence, clinical and laboratory features of coagulopathy during PPH. A summary of data collection is illustrated in figure 4 and further described in section 12.5.

Figure 3: Data collection for the E-Fib study

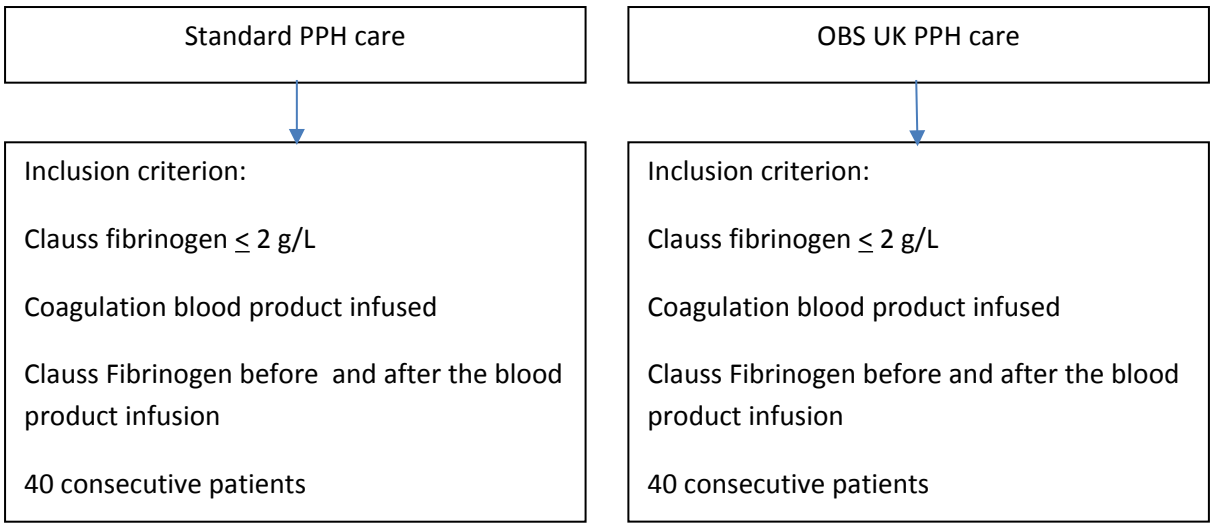
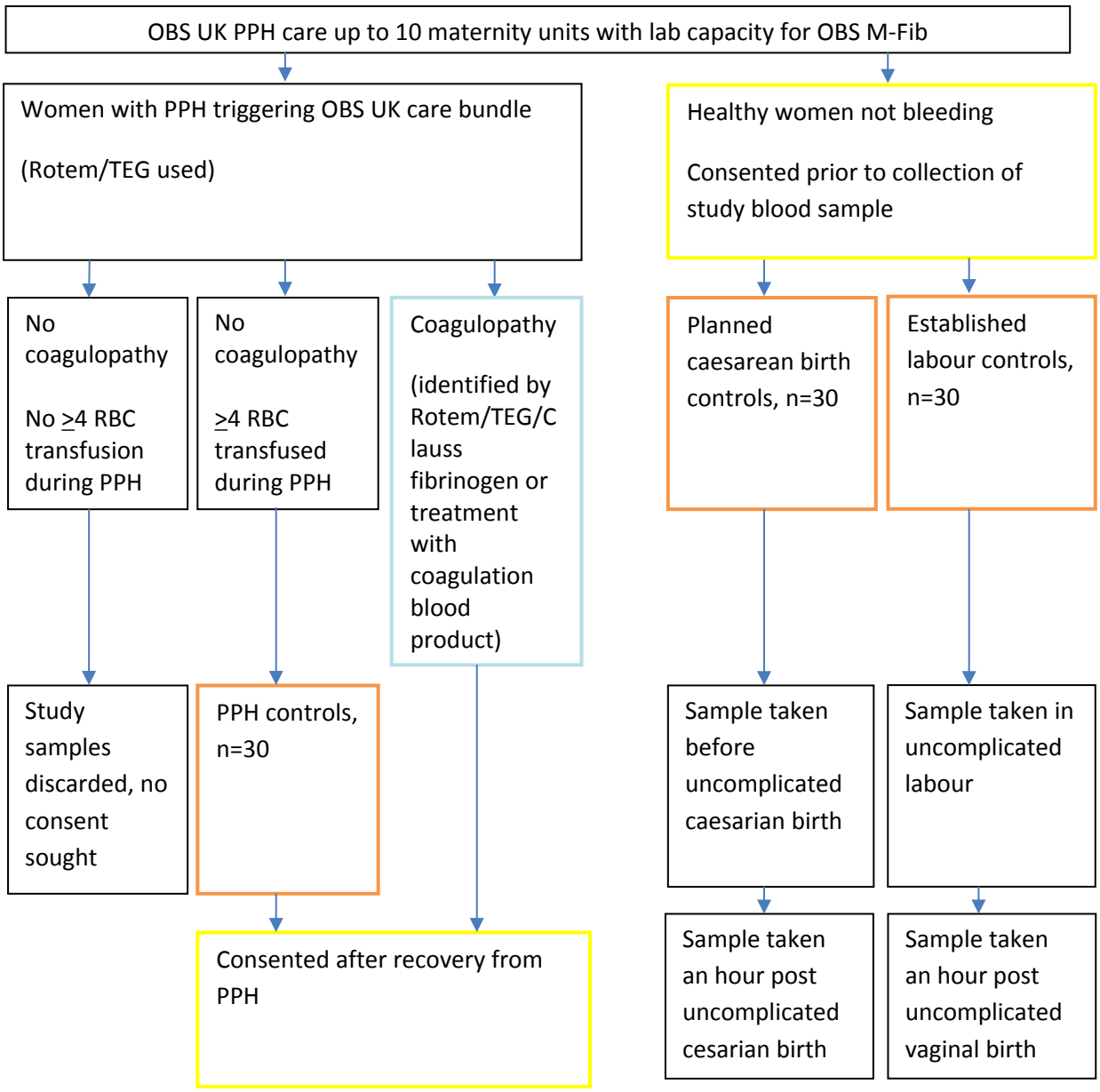


Figure 4: Data collection for the M-Fib study



*recruits with at least one stored study sample

6. Trial design and setting

6.1 Trial design

The OBS UK study is a stepped wedge cluster randomised trial involving about 189,000 women giving birth at 36 maternity units (sites) with nested psychological and cost effectiveness studies and a process evaluation to explore implementation of the intervention.

Maternity units will be randomised to one of six sequences (see Section 9.5). Maternity units will initially collect data during a period of standard PPH care for between 3 and 18 months, depending upon the outcome of randomisation. In the first sequence, 6 maternity units will collect standard care data for 3 months. They will then undertake the 9-month implementation period. The second sequence of 6 maternity units will collect standard care data for 6 months. They will then undertake the 9-month implementation period. Subsequent sequences will undertake the implementation period after 9, 12, 15, and 18 months standard care respectively. Following the 9-month implementation period, maternity units will undertake a period of data collection during OBS UK care bundle lasting between 18 (first sequence) and 3 (last sequence) months depending to which sequence they are randomised.

OBS UK intervention

The OBS UK intervention consists of all three of the following:

1. The OBS UK PPH care bundle
2. Supported by standardised documentation
3. Introduced using QI methodology over a 9-month period

See section 11 for details of the intervention.

Comparator

Standard UK care for PPH provided by maternity units prior to implementation of the intervention.

Setting

The study will take place in 36 NHS maternity units of different sizes and locations, including those serving areas of social deprivation and high proportions of ethnic minority populations.

Data collection

Data will be collected through multiple media including on-line questionnaires, interviews, submission of data to an on-line electronic database and linkage with NHS routinely collected data (see Section 12).

6.2 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a medium risk, where the level of risk is comparable to the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

7. Site and Investigator selection

The OBS UK study will recruit maternity units for assessment of the primary and secondary outcome measures. The psychology and economic sub-studies will recruit individuals. All units who are interested in participating in the trial will be required to complete a site assessment form to confirm that they have adequate resources and experience to conduct the trial and have identified a named PI and research practitioner to start the study. The research practitioner post will be funded by the study.

A QI team will need to be identified in each maternity unit, to include an obstetrician, midwife, anaesthetist and haematologist with appropriate time allocated through supporting programmed activities. The site PI may be part of the QI team, but the research practitioner cannot. The QI midwife will require 4 hours per week protected QI time during the implementation period. The time

commitment of the QI programme by the obstetrician, anaesthetist and haematologist is not defined and will vary depending on specialty, stage of the project and local factors.

The site assessment form will include the following information: annual births (the number of babies born), maternities (the number of women giving birth), and whether a site has current/prior experience of ROTEM/TEG analysis elsewhere in the hospital. The study team will record the socioeconomic and ethnic diversity of the local maternity population and whether the geographical location is inner city or a city/town with a rural catchment. The trial will recruit diverse sites reflecting the ethnic and socioeconomic mix of the maternity population in the UK.

Before a site can begin the study, a PI must be identified. The following documents must be in place and copies sent to the OBS UK Trial email account (see contact details on page 4):

- The confirmation of capability & capacity from the site's R&D department following sharing of the local information pack
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the PI
- Completed Site Delegation Log and Roles and Responsibilities document
- Appointment of a research practitioner
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- Returned copy of the Self-Evident Correction Log signed by the PI

Upon receipt of all the above documents, the Trial Manager will email written confirmation to the PI detailing that the centre is now ready to start the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive anything relating to trial intervention and a trial pack holding all the documents required to recruit into the trial. Occasionally during the trial, amendments may be made to the trial documentation listed above. The Centre for Trials Research (CTR) will issue the site with the latest version of the documents as soon as they

become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by attendance at a national virtual OBS UK launch meeting or by subsequent virtual meeting if attendance of key personnel is unfeasible.

8. Site selection

Maternity units are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. Withdrawal of sites after randomisation must be avoided if at all possible in order to reduce bias. Sites can participate in other clinical trials. Any trial studying maternal anaemia and/or intrapartum obstetric haemorrhage care would need to be discussed and agreement obtained from the Chief Investigator prior to sites agreeing to participate.

8.1 Inclusion criteria

Maternity unit

- NHS maternity units with more than 2000 women giving birth per year
- The support of the local NHS Trust maternity leaders to implement the OBS UK intervention with agreement to support QI time for the local champion team. This must include at least 4 hours/week protected midwifery time and non-clinical time from supporting professional activity for a consultant obstetrician, anaesthetist, and haematologist to participate in the QI work for the 9-month implementation period
- One Trust/ Board may contain several maternity units, if this is the case only one maternity unit per Trust/Board can be included in the study and other maternity units from that Trust/Board are excluded
- **OBS E-Fib**
  - All sites participating in OBS UK and/or OBS M-Fib sub-study can also participate in the OBS E-Fib sub-study.
- **OBS M-Fib**
  - Maternity units using the OBS UK ROTEM/TEG algorithm with laboratory capacity to process and store study samples will be considered.

Participants

- All women who give birth in participating maternity units will be included in the study
- **Psychology sub-study**
  - Women + birth partners who have experienced a PPH of greater than 1L
    - **Mental Health study**
      - Subsample of psychology sub-study. Women and birth partners who have completed the 6 month assessment reporting signs of PTSD symptoms (an IES-R score of ≥33 or score highest 25 percent of their sample via the IES-R).
      - Subsample of psychology sub-study. Women and birth partners who have completed the 6 month assessment reporting low levels of PTSD symptoms (an IES-R score of ≤22 or score lowest 25 percent of their sample via the IES-R).
- **Cost-effectiveness sub-study**
  - Women + financial partners who have experienced a PPH of greater than 1L
  - Women + financial partners who have a blood loss of less than 500mL
- **Process evaluation interviews**
  - Women and, if they would like to be involved, their birth partners (BP) who have experienced a PPH of greater than 1 L at one of four maternity units that were included in the pilot study (OBS Cymru) and selected for a site visit or at a maternity unit selected for a process evaluation site visit in the OBS UK study
  - Members of the specialist and wider team who work in the maternity service staff at four maternity units that were included in the pilot study (OBS Cymru) and are selected for a site visit or at a maternity unit selected for a process evaluation site visit in the OBS UK study
- **OBS E-Fib sub-study**
  - Women or birthing people who are infused a blood coagulation product (FFP, cryoprecipitate or fibrinogen concentrate) during a PPH and who have laboratory Class fibrinogen level ≤2g/L up to 120 minutes before blood coagulation product infusion and repeat laboratory Clauss fibrinogen level up to 60 minutes after.
  - Eligibility for E-Fib can be identified retrospectively by screening OBS UK Target source data.

- **OBS M-Fib sub-study**
  - Women with obstetric bleeding treated with the OBS UK care bundle and any of the following:
    - ROTEM Fibtem <9mm
    - TEG Citrated Functional Fibrinogen Maximum Amplitude by 10 minutes (CFF MA A10) <17mm
    - Clauss fibrinogen ≤2g/L
    - Infusion of a blood coagulation product (FFP, cryoprecipitate or fibrinogen concentrate)
    - Transfused ≥4 units allogenic red blood cells
  - Healthy women who are not bleeding including uncomplicated pregnancy before planned caesarean section (control group 2) and in established labour (control group 3)

8.2 Exclusion criteria

Maternity unit

- Maternity units that have adopted the entire OBS UK PPH care bundle
- Maternity units that have a point-of-care viscoelastic device on delivery suite or in the obstetric operating theatre

Participants

- Women who have chosen to opt out of national level data processes or the OBS UK study alone will be excluded from national and targeted source data collection and the OBS E-Fib study, but may choose to consent for psychology, cost-effectiveness, process evaluation or OBS M-Fib study components

- **Psychology and cost-effectiveness sub-studies**
  - Individuals who lack capacity to consent
  - Prisoners
  - Age <16 years
  - Women and birth partners (BP) who have had experienced a stillbirth or neonatal death
- **Mental Health study:**
  - Individuals who have not taken part in the psychological sub study

- Individuals who have taken part in the psychological sub-study but did not consent to be contacted for further research

- **Process evaluation interviews**
  - Individuals who lack capacity to consent
  - Prisoners
  - Age <16 years
- **OBS M-Fib**
  - Age <16 years
  - Individuals who lack capacity to consent
  - Prisoners
  - Women with an inherited bleeding disorder and or women who are therapeutically anticoagulated, because these women have haemostatic impairment before bleeding commences and should have a bespoke haematology plan which should not be changed by participation in the study

9. Recruitment, Screening and registration

9.1 Participant identification

Routinely collected data retrieved from NHS databases will provide trial outcome data for all women giving birth in participating maternity units. Women experiencing specific clinical outcomes caused by obstetric bleeding will also be identified by the local research practitioner (further details in Section 12).

Potential eligible reasonably consecutive participants for the psychology sub-study and the cost-effectiveness questionnaires will be identified by the routine clinical staff at the maternity unit who will inform the study research practitioner.

Potentially eligible participants for the mental health sub-study will be identified by the study team from those participants who took part in the psychological sub-study. This includes those who have consented to be contacted for further research and who have completed the 6 month assessment.

Potential eligible patient participants for the process evaluation will be identified by the local maternity unit clinical teams in collaboration with the local QI team. All potential staff participants will be identified by the local QI team.

9.2 Screening logs

For the psychology, cost effectiveness, M-Fib sub-studies and the process evaluation, a screening log of all ineligible and eligible but not consented/not approached individuals will be kept at each site so that any biases from differential recruitment can be detected. When at site, logs may contain identifiable information but this will be redacted prior to being sent to the CTR. The screening log will be sent to obsuk@cardiff.ac.uk every month during the recruitment periods (see section 19 for further detail on data monitoring/quality assurance).

9.3 Expected recruitment rates

See section 14.3, Sample size.

9.4 Informed consent

Clinical and economic outcomes

Individual consent for standard care, implementation and OBS UK PPH care will not be sought because the change in management will be delivered at a maternity unit level to all women giving birth at that site. Aggregate primary outcome data will be reported by sites for all women giving birth. The development of a research database using routinely collected national maternity datasets linked to targeted source data will allow an in-depth analysis of the primary and secondary clinical outcomes, demographic and obstetric variables, economic, psychology and E-Fib outcomes and process measures, to support interpretation and generalisability of study results. The use of identifiable data for linking purposes without individual consent is justified for the following reasons:

a. The requirement for individual consent would lead to an incomplete sample with selection bias. Women with more severe bleeding and poor outcomes (neonatal and or maternal) would be more likely to be omitted from the study
b. Specific outcomes need to be assessed locally to ensure that they are due to obstetric bleeding as this will not be clear in the national datasets
c. Process measures need to be reported for women experiencing specific outcomes, to understand changes in care that may impact the primary outcome
d. We will only request the minimum data required but this is essential data to inform the trial outcomes

e. The process for linking PPH-specific individual clinical data held by Cardiff University on trial participants to health data (sourced via NHS Digital) and deposited in a TRE will follow an established secure method for pseudonymised data linkage

f. The costs required to obtain written consent from every woman that experiences one of the specific clinical outcomes cannot be justified when the trial has been designed so that the data held in the TRE will be anonymous

g. It will not be practical to approach 189,000 women for consent to use routine data which will be transferred and held in the TRE anonymously

Further information regarding data collection is available in Section 12 and data management in Section 16.

Information about the study will be displayed on posters in clinical areas and official social media posting from the maternity units, including study team contact details, with further information available on request and via the OBS UK website. Translated study information will be available via the study website and via QR codes and we will work with Egality Health to produce videos. This information will include how to withdraw data via the national data opt-out process in England or the OBS UK study alone in England if women wish to do so.

In Scotland, the same justification for linking data in England is relevant. However, in addition to sites displaying information about the study on posters, those identified as having a PPH>1.5L and or receiving a blood transfusion due to obstetric bleeding will be provided with an exact replica of the poster, but in a small size e.g. A5, A6 or A7 This 'smaller sized' information about the study will be handed to women and birthing people in the target source data group (PPH > 1.5L and or receive a blood transfusion due to obstetric bleeding) at an appropriate time following the PPH. A record of handing the replica of the poster to women and birthing people should be recorded in the participant's hospital notes (either electronic or paper). There is no national opt-out in Scotland so this method will allow those recruited in Scotland to opt-out of the OBS UK study alone if they wish to do so.

In Northern Ireland, consent to collect pseudoanonymous data will not be sought.

Psychology sub-study and cost-effectiveness sub-study questionnaires

Reasonably consecutive women giving birth at maternity units who are eligible to be included in the psychology and cost effectiveness sub-studies will be identified by their clinical team. When these women have recovered from the acute bleed (and/or birth), they will be approached at an appropriate time, whilst an inpatient, by the research team and provided with an information sheet containing a QR code, which they can use to access the electronic consent form and questionnaires, following discharge. Contact with the partner (EP and/or BP) will initially occur via the mother, who will be provided with information sheets for the partner (EP and/or BP), again, containing a QR code which can be used to access the electronic consent form and questionnaires. Women without a partner (EP and/or BP) will be eligible to participate in all questionnaires, as will women whose partners (EP and/or BP) do not consent and vice versa. The two sub-studies will be explained and the woman and their partner (EP and/or BP) will be given a participant information sheet. Only partners (BP) that were present during birth will be eligible to complete the psychological questionnaires and this will be explained during the consent process. Only partners (EP) that live or contribute financially with the women who gave birth will be eligible to complete the economic questionnaires and this will be explained during the consent process. Mothers and partners who had a PPH will be offered £50 voucher and mothers and partners who did not have a PPH will be offered a £15 voucher following completion of the 6 month questionnaire as a thank you for their time. The £50 offer for PPH will be backdated for those who have already completed it.

After allowing sufficient time to consider the information, the participant's written or telephone or electronic informed consent must be obtained using the sub-study Consent Form prior to any study procedures taking place. Participants will be asked if they consent to be contacted in the future for other research projects.

To recruit partners to the sub studies we will approach and consent them if they are present on the postnatal wards wherever possible. Where this is not possible we will send the woman home with a patient information sheet which will direct partners to the bespoke database should they wish to take part. Following a few filter questions to identify whether they are the birth and/or economic partner they will be asked to provide online consent to take part in the sub studies. The same approach will be taken if a woman is not able to be consented on the ward and she will be asked to consent online. Participants will be asked if they consent to be contacted in the future for other research projects. At

point of consent some basic demographic and contact details will be collected. Where possible participants will be sent a text reminder and a letter or phone in advance of their survey due date to remind them that they are due to be contacted shortly and to provide them a link to access the survey.

The ethnicity and socioeconomic status of the women recruited at each site and in each study period (standard care or OBS UK care) will be recorded and reviewed jointly by the national study team and the local team after 10 women have been recruited. If the first 10 women recruited are not representative of the local population in terms of representation of minority groups, a targeted approach to subsequent recruitment will focus on these groups. A summary of the psychology and economic sub study recruitment is illustrated in Figure 5.

Safeguarding: The Participant Information Sheet will state that a) psychological data will not be analysed until at least 6 months after birth, b) the data will be anonymised and c) completion of the questionnaires is not a route to accessing support services. The Participant Information Sheet and the questionnaires will signpost to sources of psychological support. During the consent process, this information will be reiterated by the research practitioners and online (if remote consent) but if women are identified as requiring support, they will be helped to access local services through the responsible local maternity care team.

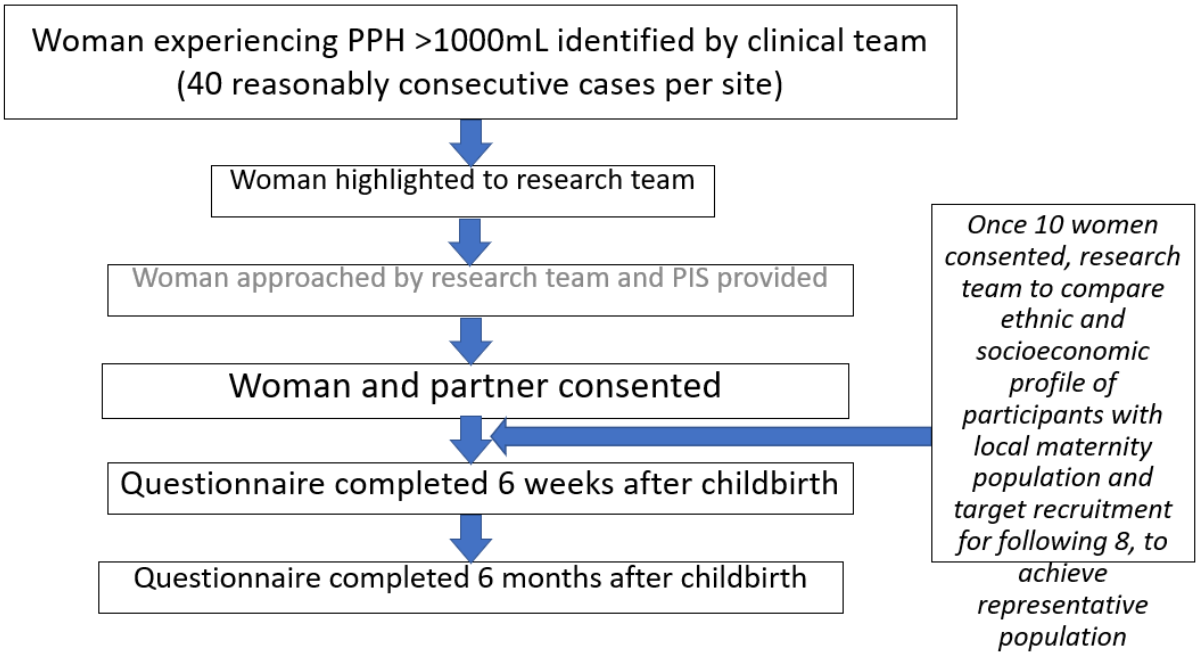


Figure 5. Psychology and economic sub-study

Mental health study

Participants in the psychological sub study who meet the inclusion criteria for the additional mental health study will be approached by the national study team to take part. To assess eligibility, the national research team will access participant details via the study database to check whether the participant has consented to be contacted for future research and completed their 6 month assessment. Of those potentially eligible, participants will be purposefully sampled based on:

1. PTSD symptoms experienced at 6 months (i.e. high levels vs low levels reported as per the Impact Event Scale score of ≥33 or ≥ 25% of top scores of the sample or ≤22 or ≤ 25% of bottom scores of the sample).
2. Ethnicity (to be as representative as possible of our study sample). Where possible we will also sample a range of participants ages and relationship status. Participant groups will not be matched.

Sampled participants will be contacted by post or email with a brief explanation for the follow-up and a copy of the PIS and consent form and alerting them that a researcher will be calling to discuss the study, During the call they will have an opportunity to ask any questions about the study and have these answered to their satisfaction. If they show a willingness to take part the researcher will go through the information sheet and consent form and arrange a provisional date for interview. Consent will be collected either verbally and recorded separately as an encrypted file, or written via post or email (whatever is most convenient for the participant) before the interview. If written consent is taken, a copy will be kept locally by the study team and another copy returned to the participant. Interviews will take place via the phone or online. Should participants not attend the scheduled interview appointment three follow-up attempts will be made.

E-Fib/M-Fib

Participants with obstetric bleeding

We propose adoption of the consent procedure that has been used successfully in our previous PPH studies [51, 53]. In women or birth people who met the OBS M-Fib inclusion criteria, double-spun samples for research will be stored until the individual has recovered from the acute bleed and is able to consider whether they wish to participate. This model of consent has been used because it is not appropriate or feasible to seek antenatal consent from all women in the maternity population as the vast majority would not be involved in the study. It is not appropriate to seek informed consent at the time of severe haemorrhage since the woman is bleeding and acutely unwell and this will preferentially exclude those with the most severe bleeding.

Once the woman/birth person has recovered from the acute bleed they will be approached and given a Participant Information Sheet about the OBS M-Fib study. They will have an opportunity to ask any questions about the study and for these to be answered. After this, written consent will be requested to store the research coagulation plasma samples in the local laboratory and then transfer these to central laboratories for specialised tests of coagulation and to use clinical, maternity and neonatal data of the person giving birth and their baby(s). The samples will be destroyed at the end of the study period after planned coagulation studies have been completed.

If research samples are taken and the woman or birth person does not fulfil the OBS M-Fib inclusion criteria these samples will be discarded.

Healthy women with no bleeding

Women who meet the inclusion criteria for collection of control samples in the M-Fib sub-study will be identified and approached for consent in the antenatal period, prior to sampling see Figure 4: Data collection for Mechanistic (M-Fib) studies.

These women will be given the Participant Information Sheet and have an opportunity to consider the information regarding the study and have their questions answered, prior to being asked to sign a consent form.

Permission will be requested to take study blood samples (5-10mL or one-two tea spoons), store and transport **double spun plasma samples** to specialist coagulation laboratories for extended tests of coagulation. If consent to participate in the study is given, demographic and maternity data will be recorded.

At sites participating in the M-Fib sub-study, when the M-Fib study is initiated the standard OBS UK posters will be substituted by OBS M-Fib posters. The posters will have links (website address and QR code) which will lead to the study website where further information will be available. Cardiff and Vale University Health Board has already implemented OBS UK care. This maternity unit will take part in OBS M-Fib and OBS E-Fib studies and bespoke posters will be displayed in all relevant clinical areas.

Process evaluation study observations and qualitative interviews

Study observations

Study posters will be placed in prominent positions in the maternity units letting staff and women know that a researcher is currently observing the unit.

Additionally, instead of taking formal consent per woman, the maternity team will let women know verbally that there is a female researcher present, giving them an opportunity to decline in case they feel uncomfortable.

The researcher will also be taking photographs of objects such as equipment, charts, wipe-clean boards and information materials that are often displayed on the walls of delivery rooms and theatres regarding PPH management as these are meant to assist care providers when managing obstetric bleeding. The researcher would also take photos of the rooms themselves as the orientation, size and configuration of the space may influence how PPH care is implemented. In no circumstances will these photographs include people or confidential information. They will be used to help the researcher recall the context of the site visit in order to describe it accurately, but will not be used themselves in the presentation of results or in any publications of study results. The photographs will be stored on servers at the University of Oxford alongside other process evaluation data. The photographs will be uploaded to and stored on servers at the University of Oxford alongside other process evaluation data and interviews. University of Oxford are named on the Data Protection Impact assessment (DPIA) as an organisation that will be processing and storing data in the trial. Once uploaded, photographs will be deleted from the device used to capture them. They will be stored in password protected folders on the secure server. The data will be stored for 15 years in line with other process evaluation data.

Interviews

Women (and if they would like to be involved, their birth partners, BP) who have given birth at the maternity unit and who have experienced a bleed of more than 1L (identified as potential participants by the local maternity team, in consultation with a member of the process evaluation team) will have the study explained while still an inpatient, will be given a Participant Information Sheet and will be given the opportunity to have all their questions answered satisfactorily. If they agree to participate, they may choose to be interviewed while still in hospital or share their contact details with the member of the process evaluation team, to be contacted by them a few days after discharge from hospital to set up an interview over the telephone or online, at a time that is convenient to them. Before the interview, consent will be sought by the researcher from the national process evaluation team and they will be asked to sign an informed consent form or give verbal remote consent (which will be recorded). One copy of the consent form will be given to the participant and the original copy will be kept in the investigator site file. A further copy should be kept with the participant's hospital notes, if appropriate.

Multi-professional staff groups at the maternity units will be identified by the local QI team and then approached by a member of the national process evaluation team. The study will be explained and a Participant Information Sheet given to them to read. If they agree to participate they will be asked to sign a consent form. Consent may be taken verbally if the interview is over the telephone or via video conferencing, and will be recorded.

The rights of participants to decline to participate in any sub-study without giving reasons will be respected. Similarly, the participant will remain free to withdraw at any time from the sub-studies without giving reasons and without prejudicing his/her further treatment or staff status. However, participants will be advised that once participant de-identified data has been incorporated into the body of the analyses then it may not be possible to completely destroy all of their data illustrative quotes from their interview will not be used in any outputs.

During the case studies, the process evaluation team will seek advice from local clinicians/managers or the study steering committee as appropriate should issues (e.g. confidentiality, safeguarding) arise.

9.5 Randomisation

Maternity units will be randomised to one of six sequences before the start of the study, with size of maternity unit (births per annum) included as a balancing measure. In addition, half the sites in each sequence will be allocated to use the ROTEM point-of-care coagulation device and half to use the

TEG point-of-care device. If a ROTEM or TEG is already in use in another area of the hospital, then the same device will be allocated to the maternity unit to improve familiarity of use and interpretation of the device, if possible. If a ROTEM or TEG is not in use in the hospital then a device will be randomly allocated to the site ensuring that an equal number of each device is allocated across the 36 sites. However, overall half the sites will be allocated to ROTEM and half to TEG and so some sites may need to use an unfamiliar device. Randomisation of sites into sequences and allocation of ROTEM or TEG device will be performed by the study statistician at the start of the data collection period. Details of the randomisation process will be specified in a separate randomisation plan.

10. Withdrawal & lost to follow-up

10.1 Withdrawal

Women in England may opt out of the national dataset by using the NHS Digital National Data Opt out process in England. This will not affect care but is applicable to all research studies purposes, not just the OBS UK trial. Any data opt out request will be applicable if the request is received before the routine data for that individual woman has been transferred to the Trusted Research Environment from the national routine data sources. In order to avoid including women who have opted out of data collection through the national data opt service, sites will use the NHS MESH (Message Exchange for Social Care and Health) service to provide a list of the relevant NHS numbers to be checked against the national data opt-out repository. The site will receive a list of NHS numbers for the records that cannot be disclosed for the individual data collection. Once the routine data has been received and processed, data will be anonymised and therefore it will not be possible to withdraw the data from the analysis. Women will also be able to opt out of the OBS UK study alone in England and Scotland but not in Northern Ireland. See opt out strategy for more information. At each study site the study research practitioner will ensure that the midwives who provide care to young women under the age of 16 are made aware of the study and opt out processes for the OBS UK study and bring this to the attention of the young women in their care.

If a participant initially consents to the sub-studies, but subsequently withdraws consent they will not be sent any further questionnaires. They will also not be contacted for any additional future research. The withdrawal of participant consent shall not affect the trial activities already carried out and the

use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

In all instances participants who consent and subsequently withdraw will be requested to complete a withdrawal form (see Withdrawal Form in trial pack and on the trial database) or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to obsuk@cardiff.ac.uk. Any queries relating to potential withdrawal of a participant should be forwarded to obsuk@cardiff.ac.uk.

OBS M-Fib

Women will have the option to withdraw from the OBS M-Fib study at any stage. If a woman withdraws from the study, data collected up until the time of withdrawal will be included in the OBS M-Fib analyses. If a woman withdraws, any remaining stored samples will be destroyed.

10.2 Lost to follow up

A participant may be lost to follow-up from the psychological/economic and process evaluation sub-studies for the following reasons:

- Non-compliance in completion of 6 week and 6 month questionnaires
- Women and partners (EP and or BP) who are not at home with their baby at the time of the 6 week or 6 month questionnaires
- Non-attendance at interviews
- Death

To minimise loss to follow up, a window of 4 week will be allowed for completion of the 6 week and 8 weeks for the 6 month questionnaires. In addition, 3 modes of contact will be requested (email, phone and address) and 3 reminders sent to each participant. Follow-up attempts will continue for two weeks only. Consent will be obtained for the participants to be sent automatic text messages and/or text messages.

11. Trial Intervention

11.1 OBS UK Intervention

The implementation of the intervention will be undertaken during a 9 month period. The timing of the 9 month implementation period depends on the sequence that a site has been randomised to.

Intervention for the OBS UK study

The OBS UK intervention will be introduced in all areas of the maternity unit including the midwifery-led and obstetrician-led units and for home births and consists of all of the following:

1. The OBS UK PPH care bundle
2. Standardised documentation for PPH management
3. A QI programme to introduce the OBS UK care bundle and standardised documentation (Appendix 1) over the 9 month implementation period

11.1.1 OBS UK care bundle

The OBS UK PPH care bundle consists for four components:

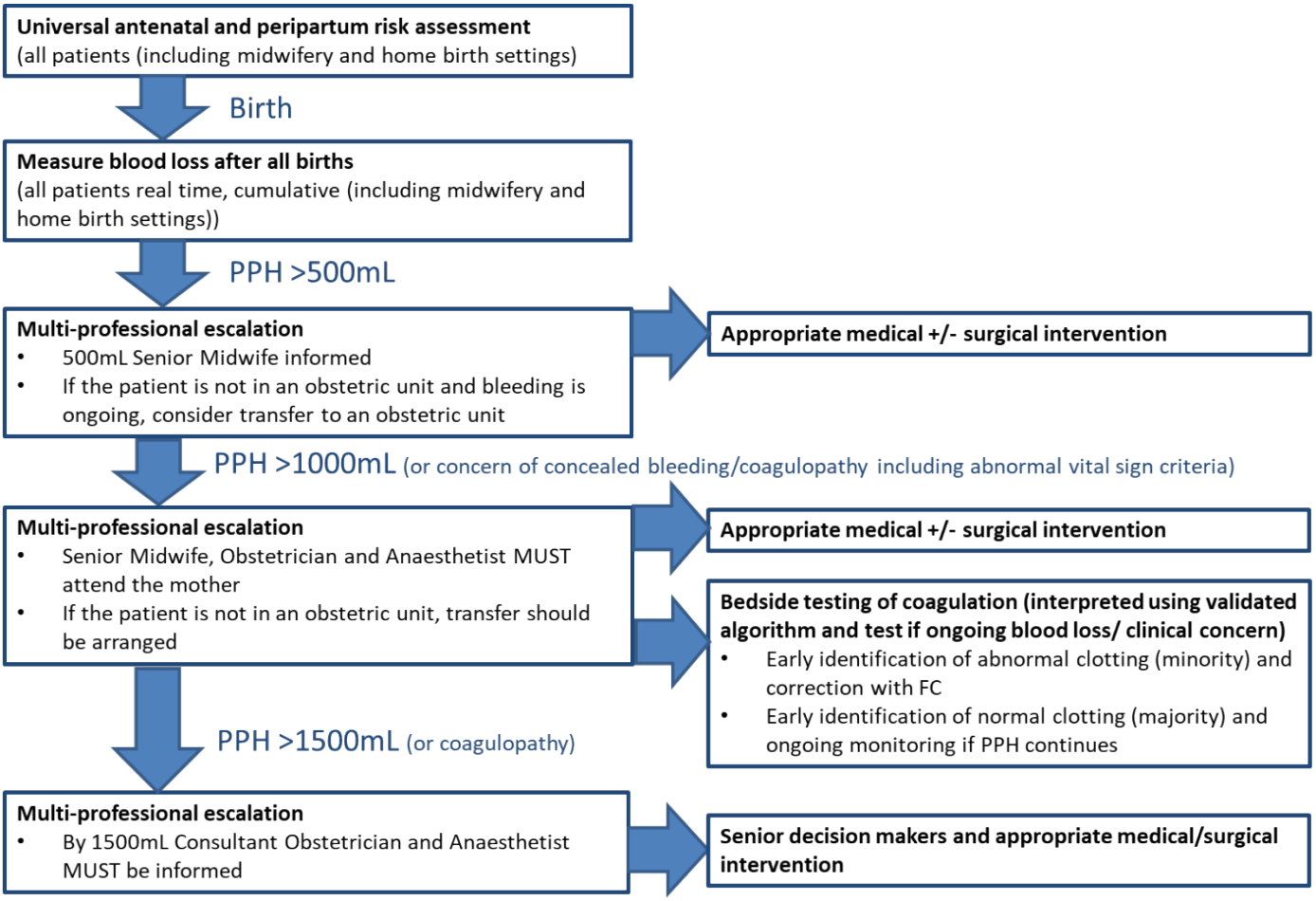


Figure 6. The OBS UK PPH care bundle

1) **Risk assessment:** Where practical a 'risk assessment' will identify a standard set of risk factors for PPH (based on RCOG guidance) and will categorise the level of risk accordingly. It will also include a set of triggers for action based upon the measured level of risk. The risk assessment will be undertaken on arrival to an obstetric-led delivery unit or when a woman is in labour. This should be re-evaluated whenever a change in circumstances occurs as the risk may change over time.

2) **Quantification of blood loss (QBL):** Where practical, cumulative blood loss will be measured objectively from the time of birth in all women giving birth at the maternity unit using a

validated method that combines volumetric and gravimetric measurements. Volumetric measurements will be derived from under-buttock drapes, drains and suction containers after amniotic fluid has been excluded. For gravimetric measurements, blood on pads or swabs will be measured by weighing and subtracting the known dry weight to give a blood loss in mL (1g=1mL). In the case of vaginal birth the under-buttock pad is removed immediately after birth to accommodate amniotic fluid and then any further fluid is included in the blood loss measurement.

3. Escalation of multi-professional care to more senior staff at defined volumes of blood loss (or earlier if low maternal weight/BMI) with appropriate medical intervention:

a. At 500 mL the senior midwife is informed. If the mother is not in an obstetric unit and bleeding is ongoing, consider transfer to an obstetric unit if this has not already happened
b. At 1L, the senior midwife, an obstetrician and anaesthetist must attend the woman to diagnose and treat the likely cause of bleeding if this has not already happened. If the mother is not in an obstetric unit, transfer to an obstetric unit should occur.
c. At 1.5L, the consultant obstetrician and anaesthetist should be informed and attend if bleeding is ongoing if this has not already happened.

4. Point-of-care test of coagulation, blood component replacement and tranexamic acid

At 1 L blood loss with ongoing bleeding a point-of-care test of coagulation should be performed and a coagulation screen sent to the laboratory for routine testing. Coagulation tests may be undertaken earlier at the discretion of the treating clinicians for any clinical concern, for example concern of haemostatic impairment, placental abruption, amniotic fluid embolism or concealed bleeding. The point-of-care coagulation tests will be performed using either a ROTEM or TEG depending on which device the maternity unit has been allocated to.

The point-of-care coagulation test should be interpreted according to the OBS UK point-of-care algorithm. The algorithm identifies reduced levels of fibrinogen and promotes early replacement with a concentrated source of fibrinogen (either fibrinogen concentrate or cryoprecipitate). If the local site decides to use fibrinogen concentrate, any brand of fibrinogen concentrate may be

used. A site may switch brand of fibrinogen concentrate during the study and may switch from cryoprecipitate to fibrinogen concentrate or vice versa at any time during the study. If deemed appropriate by the local multi-professional team, fibrinogen concentrate and cryoprecipitate may both be administered to an individual patient. The site must inform the study team if the source of concentrated fibrinogen changes and the date this occurred.

The algorithm may not be applicable for women with inherited bleeding disorders and the local team should develop an individualised delivery plan for these women according to local routine practice. The algorithm may not be applicable in cases of coagulopathy due to sepsis or in women who are taking anticoagulants.

The point-of-care test of coagulation should be repeated after each 500 mL additional blood loss, after infusion of fibrinogen concentrate, cryoprecipitate or FFP or at any time for clinical concern. The OBS UK algorithm should be used to interpret these tests and blood components infused if indicated by the algorithm.

Tranexamic acid 1g IV should be given as soon as abnormal bleeding is identified according to local protocols but must be given at the latest after 1L measured blood loss with ongoing bleeding. Tranexamic acid 1g IV should be repeated after 30 minutes if bleeding is ongoing.

Sites will be trained in the use, maintenance and quality control of the ROTEM or TEG devices by the manufacturer in conjunction with local point-of-care management teams. The national study team will train local site personnel on the interpretation of the OBS UK algorithm, and this training will be cascaded to all relevant site personnel.

11.1.2 Standardised documentation

A standardised documentation tool (PPH proforma), developed during the pilot study, OBS Cymru, will be introduced at each site during the 9-month implementation period and continue to be used during the period of OBS UK care. It may be adopted for use by all sites to align with their current documentation systems in paper and/or electronic formats.

11.1.3 Quality improvement (QI) methods

The 9-month QI programme provides the means to support the implementation of the OBS UK care bundle and standardised documentation tool and aims to change the maternity unit culture, focus on active management of PPP and de-normalise PPH within the unit.

National multi-professional QI team

A multi-professional national study QI team, consisting of midwives, obstetricians, anaesthetists and haematologists will support local sites in QI methodology, education and implementation of the care bundle. The national QI team will:

1. Organise and lead the QI site initiation meetings
2. Provide training and care bundle resources to sites
3. Support sites with local QI data collection and interpretation
4. Support sites in adopting OBS UK PPH care – cascading educational events, providing training and education materials, creating an enthusiasm for change and working with local leaders to remove barriers to change
5. Facilitate networks between sites to accelerate learning and adoption

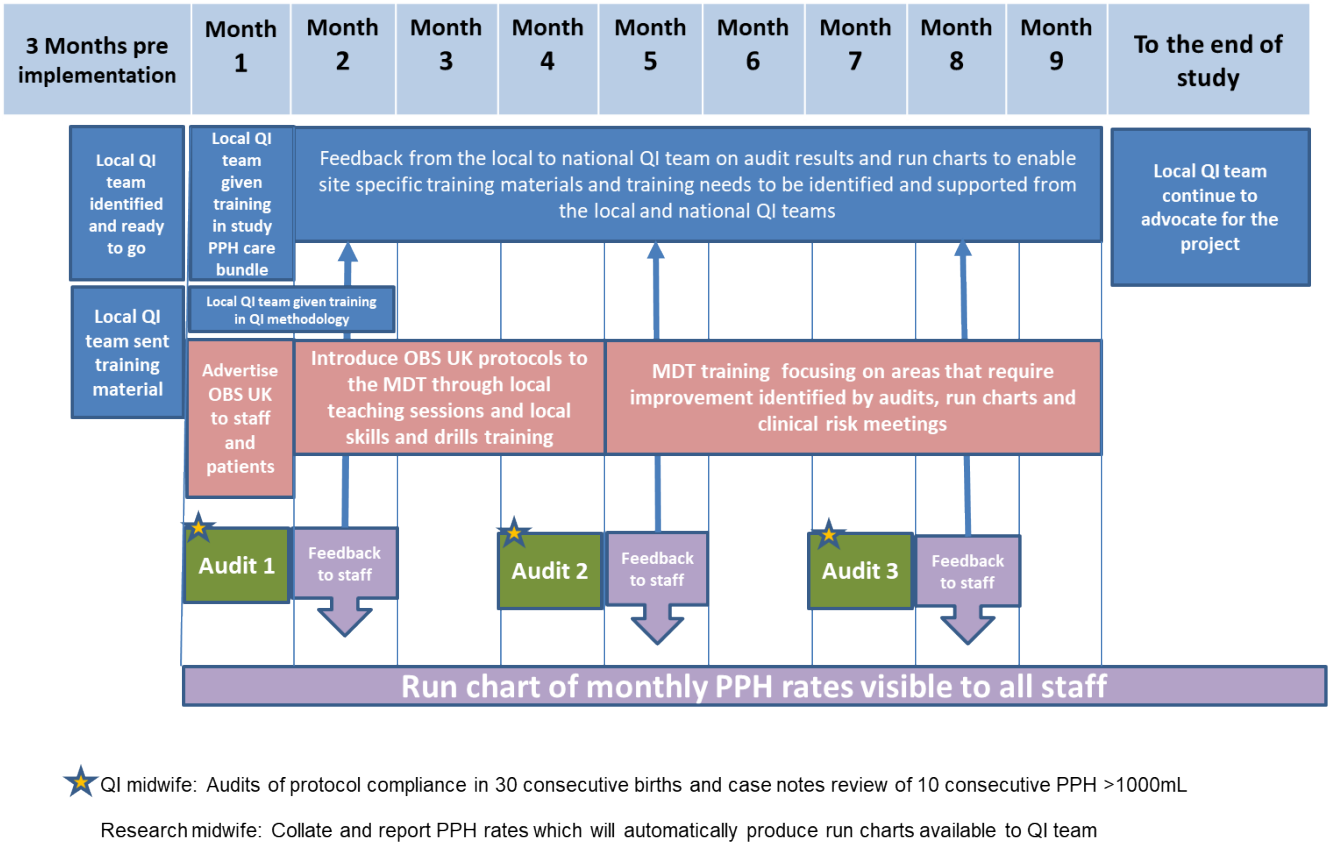


Figure 7. OBS UK 9 month implementation period

Local multi-professional QI champion teams

Each site must appoint a local QI champion team consisting of a named QI midwife, obstetrician, anaesthetist and haematologist. These four people will be the local QI champion team and will lead the introduction of the OBS UK care bundle at the site using QI methodology over the 9-month implementation period. Interpretation of the results of the audits and case note reviews at months 1, 4 and 7 of the 9-month implementation period will be a role for appropriate members of the local QI champion team, supported by the national team, and will facilitate practice change. The time for the local QI champion team will be funded by the site.

A research practitioner will be funded by the study and cannot be part of the QI team. They will collect and validate clinical outcome data and undertake other trial-related tasks, including identifying potential participants for sub-studies and seeking consent. This allows the local QI team

to focus on clinical improvement. They will repeat the audit and case note reviews the first month after implementation and at the end of the study.

QI site initiation meetings at the start of the 9-month implementation period

At the start of each sequence, the local QI champion teams from that sequence (6 sites per sequence) will attend a half-day online site initiation meeting led by the OBS UK national QI team. Ideally one half-day initiation meeting will include all 6 sites in the sequence but if this is not feasible more than one session will be provided. The initiation meeting will:

1. Introduce the OBS UK obstetric haemorrhage care bundle and associated educational material
2. Answer questions
3. Create enthusiasm for change and raise awareness of the challenges of obstetric haemorrhage care
4. Introduce QI skills to support change
5. Create networks
6. Foster a community of practice

Education and training about the components of the OBS UK care bundle

Standardised training, developed in the pilot study, will be used in the OBS UK study and introduced to the local QI teams by the national QI team. The training material covers QBL performance and interpretation of point-of-care tests of haemostasis and team PPH training. The components of the OBS UK care bundle will be implemented at local sites through 'train the trainer' sessions led by the national team followed by local cascade training led by the local QI champion teams.

The local QI champion teams will receive training in QI methodology and skills through the online initiation meetings, enabling them to interpret process and outcome data and achieve change. The local QI team will integrate training into local training opportunities including multi-professional simulation training, ad hoc sessions and monthly QI/audit sessions. Plan-do-study-act (PDSA) cycles will include measures of frequency of training, attendance, and feedback to ensure standardisation and uptake of the intervention.

Local multi-professional QI team activities during the 9 month implementation period (implementation months 1-2):

1. Advertise the project to maternity unit staff and women through local maternity voices partnerships, via online maternity unit platforms and posters in antenatal clinic settings
2. Coordinate cascade training for QBL and implement standardised escalation
3. Receive local point-of-care coagulation device which will be installed in the delivery suite or obstetric theatre combined with cascade training on the use of the machine, quality control and interpretation of the OBS UK blood component algorithm
4. Receive fibrinogen concentrate for blood banks to distribute, if appropriate for the site
5. Complete the first audit and case note reviews of obstetric haemorrhage management (see below)
6. Present initial baseline unit and audit/case note review data to local staff and use data to inform areas for change (PDSA cycles)

Local multi-professional QI team activities during the 9 month implementation period (implementation months 3-9):

1. Repeat two further audits and case note reviews of PPH management at months 4 and 7 (see below) and use these data to inform areas of change (PDSA cycles) including dissemination of uptake of the intervention and obstetric haemorrhage rates to the whole maternity unit MDT.
2. Meet with the national QI team at least twice to review progress (at about months 4 and 7)
3. Continue to cascade educational material to support adoption of OBS UK
4. Share learning from networks and maintain momentum

Local multi-professional QI team activities during the 9 month implementation period (implementation months 7-9):

The local QI champion team will plan sustainability to ensure OBS UK care becomes standard practice and inform local maternity voice groups of the change in care

Audit and case note reviews

At months 1, 4 and 7 of the 9-month implementation period the local QI team will conduct audits of 30 consecutive deliveries (all locations, not just obstetric unit births), irrespective of blood loss, and undertake case note reviews of 10 consecutive women who had experienced an obstetric haemorrhage of more than 1L. The audit will establish the proportion of women who have had a risk assessment performed and had QBL after birth. The case note reviews will identify the proportion of women with PPH who have a completed risk assessment in their notes, had QBL from the time of birth, evidence of completion of OBS UK standardised paperwork, evidence for multi-professional attendance at 1L blood loss or clinical concern and whether point-of-care tests of coagulation were performed and appropriately interpreted using the OBS UK algorithm.

The results of the audit and case note reviews and comparison with other anonymised sites will be fed back to staff on the maternity unit by the local QI champion team to inform areas for change. The audits and case note reviews will be analysed and reported as part of the process evaluation (see also Section 12).

11.2 Compliance

Implementation of the intervention will use QI methodology which includes in-built components to improve compliance. There will be audits and case note reviews at 1, 4 and 7 months of the 9-month implementation period and the results of these will be fed back to maternity unit staff to facilitate implementation. If any units fail to implement individual elements of the OBS care bundle during the 9-month period, this will be modelled in a separate sensitivity analysis. The failure to implement one or more components of the care bundle in the management of an individual woman during the implementation or UK OBS phases will not be regarded as a breach of protocol. Audit and case note reviews will be repeated in the first month after implementation and at the end of the study.

12. Trial procedures and data collection (Table 1)

12.1 Stepped wedge OBS UK study

All sites will start data collection at the same time. Data collection will start whilst all sites are providing local standard care. The duration of standard care and OBS UK phases will depend on the sequence to which the site was randomised.

Aggregate primary outcome data

The proportion of women who receive an allogenic red blood cell (RBC) transfusion for PPH will be reported by all maternity units for every month of the study (see also Section 5.3). This data will include all women. This data will be reported in aggregate to achieve an inclusive sample from which the impact of data opt out on completeness of the linked research database can be reported. In order to ensure data accuracy, data will be compiled from both maternity and blood bank records.

Targeted source data

At least once a month, during the study the research practitioner from each site will identify and send targeted source data for women who experience PPH >1.5L and or receive a blood transfusion due to obstetric bleeding. This is to ensure that primary and secondary trial outcomes are due to PPH and develop a research database using routinely collected national maternity datasets linked to target source data for in-depth analysis of clinical outcomes, demographic and obstetric variables, economic and psychology outcomes and process measures. The targeted source data is not consistently reported in routine data sources, but is routinely collected in individual notes, electronic case records and local maternity, blood bank, haematology laboratory, ROTEM/TEG devices and the Intensive Care National Audit and Research Centre (ICNARC) databases. In English sites, data from women who have opted out of national data use or OBS UK alone will not be transferred to the OBS UK database and local research practitioners will confirm this (Section 16.1.3). In Scotland, data from women who have opted out of data for use in the OBS UK study will not be transferred to the OBS UK database. In Northern Ireland, pseudoanoymised routine data will be transferred to the OBS UK database.

If there is uncertainty about the indication for the outcome, the local PI will decide whether it was for obstetric bleeding or not. The targeted source data will include:

1. **Primary and secondary clinical outcomes**
    a. **Blood transfusion:** All women transfused allogeneic red blood cells and the number of units, or cell salvage red blood cells and the volume within 4 hours prior to birth up until discharge
    b. **Other blood components/products transfused:** Number of women transfused coagulation products including type of product (FFP, cryoprecipitate, platelets or

fibrinogen concentrate) and number of units for obstetric bleeding within 4 hours before birth up until discharge

c. **Coagulopathy:** Most abnormal fibrinogen, PT/APTT, platelet count, ROTEM or TEG to define coagulopathy as the number of women with fibrinogen levels ≤2g/L, ROTEM Fibtem A5 <9mm or TEG CFF MA (by 10 minutes) <17mm, PT/APTT >1.5x midpoint of normal reference range and platelet count <75 $x10^9$ within 4 hours prior to and 24 hours after birth
d. **Haemostatic surgical and radiological interventions:** Number of women requiring uterine tamponade balloon insertion, uterine brace suture, transfer to theatre or any radiological intervention for PPH
e. **Hysterectomy:** All women receiving hysterectomy for PPH between birth up until hospital discharge
f. **Maternal death:** Any woman who dies following PPH
g. **Higher level of care:** All women transferred to higher level of care outside of the obstetric unit for complications following PPH.
h. **Cardiovascular shock**: All women transferred to higher level of care outside of the obstetric unit for vasopressor infusion following PPH.
i. **Organ dysfunction**: All women transferred to higher level of care outside of the obstetric unit for organ support following PPH.
j. **Breastfeeding**: Time and type of first feed
k. **Duration of hospital stay**: Time from birth up until discharge
l. **Neonatal death and stillbirth rate:** Number of neonatal deaths and stillbirths

2. **Process measures** (see process evaluation section below)
3. **Demographic and obstetric characteristics including:** ethnicity, parity, body mass index, age, induction or spontaneous onset of labour, mode of birth, location of birth, volume of blood lost at birth, date and time of birth (new baby), gestation at birth, and cause of PPH, sickle cell disease.

Routine data sources

At least two data requests from NHS Digital and Scottish equivalents will be made (one to check linkage processes and plan statistical cleaning and coding and one to import all data from the whole study period and conduct analyses). This will provide data for the cost-effectiveness sub study and for analysis of maternity care provision over the course of the study which change and affect the primary outcome. Data will be requested from NHS Digital Databases (including Hospital Episode Statistics, Maternity Services Dataset, Children and Young People's Health Services Dataset, Child Health Surveillance System and from Scottish equivalents) to provide:

1. Demographic and obstetric characteristics of all women giving births to include deprivation index, ethnicity, parity, body mass index, age, induction or spontaneous onset of labour, mode of birth, location of birth, volume of blood lost at birth, date of birth (new baby), gestation at birth,
2. Duration and intensity of antenatal, intrapartum and postnatal care, maternal surgical procedures and complications,
3. Maintenance of breastfeeding including exclusivity at 6 weeks.

12.2 Psychology sub-study

If a woman and/or their birth partners (BP) agree to participate in the sub-study they will be asked to complete EPDS and IES-R questionnaires at 6 weeks and 6 months. The local research practitioner and/or automatic text messaging where possible will prompt the participants to complete the questionnaires at the appropriate times. The questionnaires can be completed on-line or by telephone (for women unable to read written information and or do not have access to digital media, as identified during the initial consent). Prior to completion, respondents will be prompted online to reconfirm consent and eligibility.

The research practitioner will complete the CRF which will include the ethnicity, socioeconomic group and details of the birth. This will be uploaded into the study database.

At 6 weeks, where possible automated text messages and questionnaires will be sent to mothers and partners (BP). The questionnaire will specifically ask the woman and her partner (BP) “Did you feel you/your partner was at risk of death or serious harm”, yes/no. In addition, semantic differential questions will be asked to identify interpersonal factors associated with the experience of birth as traumatic to capture communication with the clinical team, confidence in staff and atmosphere of the clinical area. These items, which will number no more than 12 will be designed from the

literature and from discussions with the PPI group. We will also explore breastfeeding in the psychological questionnaires using the following questions:

Initiation (6 weeks questionnaire): Problems with breastfeeding can be more common among women who bleed heavily during birth. There are several reasons for this. On occasions the start of breastfeeding is delayed, or the woman feels too unwell to breastfeed her baby. For some women milk production is reduced. As breastfeeding is important to many women, we would like to ask about your experiences of feeding your baby.

Was your baby's first feed:

Breast feed only

Bottle feed only

Combined breast and bottle feed

How soon after birth was your baby first fed?

Within an hour

Between 1 and 3 hours after birth

More than 3 hours after birth.

Did you initiate breastfeeding within one hour after birth?" YES/NO .

2. Maintenance and Exclusivity (6 weeks and 6 months questionnaires)[22]:

a. "Are you still breastfeeding your baby/babies exclusively" YES/NO

b. "Are you still breastfeeding your baby/babies in any quantity?" YES/NO

if NO: "If you no longer breastfeed in any quantity, for how many weeks did you breastfeed in any quantity?"----------

if YES: please complete the scale below for last 48hrs for current status: (100% formula fed to 100% breastfed)

3. At 6 months, where possible automated text messages and questionnaires will be sent to the mother and/or birth partners. The questionnaires for mothers and their partners (BP) will ask whether they have tried to access professional support or intervention for psychological symptoms related to their birth experience, what, if any, support they have accessed and their views on this.

We will investigate whether women, in relation to their birth experience and its aftermath, have sought or been provided with any specialist care from the following:

1. Maternity review by a midwife or obstetrician
2. General primary care services via their GP or health visitor
3. Been referred or self-referred to Improving Access to Psychological therapy (IAPT) or a counsellor
4. Been referred or self-referred to a specialist maternity /perinatal psychologist or psychiatrist.

We will distinguish between these 4 levels of service and also what was provided in terms of: general listening, active psychological therapy and medication. We will also note the number of sessions and the process of instigation of input. Finally, we will record women's views on the utility of the received provision in terms of how helpful it was in resolving difficulties, ranging from not helpful at all to extremely helpful.

12.3 Mental health study

If a woman/birthing person or birth partner agrees to take part in the mental health study they will be asked to take part in an individual semi structured interview either on the phone of via the internet. We will seek to interview a minimum of 10 women/birthing people who reported high levels of PTSD at 6 months (assessed as a score of 33 or more via the Impact of Event Scale-Revised or the top scoring 25% of the study sample) and 10 who reported low levels of PTSD symptoms (assessed as a score of 22 or less via the Impact of Event Scale-Revised or lowest 25% of scores of the study sample). In addition we will also seek to interview a minimum of 10 birth partners with high levels of PTSD symptoms or the top scoring 25% from the study sample and 10 with low levels of PTSD or the bottom scoring 25% from the study sample. Interviews will typically last no more than 1 hour and will be scheduled for a time convenient for the participant. Interviews will explore their experiences of the PPH, the care provided during and immediately after their bleed whilst still in hospital, after discharge and once discharged from maternity care. The interview will seek to understand the participants perspective of protective and harmful experiences and what could have helped to improve their care and reduce distress at each time point. Interviews will be audio recorded and transcribed verbatim. Data from the PTSD symptomatic and non-symptomatic groups will be analyses separately using Template Analysis[55]. The initial outline template will include the following: how participants experienced the PPH, what made the events of the PPH most stressful and what aspects facilitated coping, how they were cared for during the PPH, immediately after and postnatally and their thoughts and feelings about what hindered and what could have improved

their experiences. The PTSD and No PTSD groups of women/birthing people and partners will be compared for consistencies and differences in emergent themes and subthemes. To ensure appropriate identification and labelling of the constituent themes we will employ repeated checking of the evidential basis and engage PPI panel members to contribute to this process.

12.4 Cost-effectiveness sub-study

The women and partners (EP) recruited to the psychology sub-study will also be asked to complete an EQ-5D-5L health-related quality of life questionnaire at 6 weeks and 6 months postnatally. The same women and partners will be recruited for both sub-studies, although only BP will be eligible for the psychology study and EP for the cost effectiveness study. In addition, the cost effectiveness study will recruit women and partners (EP) who did not experience a PPH before and after the intervention.

Using routinely collected data from NHS England and Scotland, the national study team will also undertake a bottom-up micro-costing in a sample of maternity units that identifies, measures and values medical, midwifery and support staff costs and consumables associated with risk assessment, monitoring blood loss, testing blood clotting, escalation procedures and follow-on management. Cost apportionment of implementing the intervention at patient level will account for the size and clinical composition of the maternity unit. A separate analysis plan will be completed before data collection is initiated.

12.5 Process evaluation

Prospective data from all sites

a. Surveys

i. **Site context questionnaire.** At the start of the OBS UK study, all sites will complete an on-line questionnaire to investigate site context. This will include multiple variables such as demographic characteristics of the population giving birth including ethnic diversity and social deprivation, staff training and education, obstetric haemorrhage protocols, cell salvage practice, clinical risk processes and staffing. This will be completed by the research practitioner, supported by the PI.

ii. **Online staff survey at end of the 9 month intervention period.** Multi-professional teams and champions will complete this to describe activities

and overall experience of the intervention (including relevance, applicability in context of site, staffing, patient demographics). The survey will also explore whether intersectional identities within teams and across staff and patients affect their experiences. This will further describe mechanisms of impact, fidelity, compliance and variation according to site context.

b. QI measures

i. M**onthly run charts.** To inform the QI progress, aggregate monthly PPH data (PPH volume and red blood cell transfusion) will be collated by the research practitioner, inputted into the OBS UK Trial Database and shared with NHS staff throughout implementation and the OBS UK period to inform and understand change.

ii. **Audit and case notes review during implementation (1, 4 and 7 months).** Audit (30 consecutive births) and case notes review (10 consecutive cases where blood loss greater than 1L was recorded) data will be collected by local QI teams and analysed by the local QI team and national study team to examine the adoption of the components of the OBS UK care bundle. Aggregate results of audit and case notes review will be entered into the OBS UK Trial Database and shared with NHS staff throughout implementation and the OBS UK period to inform and understand change.

iii. **Audit and case notes review in 1st month after completion of implementation**.

iv. **Sustainability assessment.** At the end of the study a further audit and case note review will be undertaken at all sites and the results submitted to the study database. These data will be used to study the natural decay of components of the OBS UK care bundle after the end of the 9-month implementation period.

v. **Process measures**. It is important to collect and analyse process measures for both standard and OBS UK care, as failure to detect a difference may be due to changes in care which impact on the primary outcome (eg. management of antenatal anaemia and timing of clinical escalation). Targeted source data will therefore be extracted from the woman's health care record (electronic

and or notes) for women who bleed >1.5L and/or receive a blood transfusion for PPH (see section 12.1):

1. Most recent platelet count and haemoglobin level ($x10^9$, g/L) prior to obstetric bleeding, date
2. First platelet count, fibrinogen, PT, APTT, TEG CFF MA (by 10 minutes)/ROTEM Fibtem A5 level during obstetric bleeding/concern of bleeding ($x10^9$, g/L, secs, mm), date and time
3. Lowest haemoglobin level (g/L) during obstetric bleeding/concern of bleeding
4. Last haemoglobin level (g/L) prior to discharge
5. Medical review if bleeding started/concern of bleeding occurred before birth, time and date
6. Transfer to theatre for PPH, arrival time and date

c. **Case studies**

Four maternity units that took part in the OBS Cymru pilot study will have site visits from the national process evaluation team. These visits will be performed before the 30 month stepped wedge OBS UK study data collection starts. Twelve maternity units in Wales implemented the OBS UK intervention in 2017-2018 in the pilot study, OBS Cymru. Since it will be 5 years since the pilot study was conducted, exploring how obstetric haemorrhage management occurs now, including if there are process changes and staff insights, will be useful to understand longer term sustainability, help to anticipate barriers and optimise delivery of the OBS UK intervention. The national process evaluation team will make ethnographic observations (over 2-3 days per site) and undertake qualitative interviews with clinical leads, maternity staff and mothers (5-6 staff interviews, 2-3 patient interviews, per site).

Prospective case studies will be performed at 6 sites (one site per sequence) by the national process evaluation team. Sites will be chosen to represent maximum variation in geography, deprivation and ethnic composition of women and staff. Interviews conducted as part of the process evaluation will utilise online translation services, when required, which are available for all languages. The 6 sites will each be visited during the standard care period, the implementation 9-month period and the OBS UK care period making three visits per site. The dates for the site visits will be agreed with the local principal investigator and research practitioner. The visits during the standard care and OBS UK care

periods will last 3-4 days and include observations during routine working hours and outside of routine hours, including at night. During the implementation phase, the process evaluation researcher will accompany the OBS UK implementation team on their site visit and observe their meetings with the local site teams. They will also observe the OBS UK online training sessions delivered to the case studies teams over MS Teams. These observations collectively will allow time-sensitive exploration of variation in care provision, QI activities and implementation. Case studies will examine the role of context, such as due to service configuration, geography, deprivation, ethnic composition of staff and patients and other intersectional socio-demographics in professional, interpersonal and clinician-patient interactions, team dynamics and atmosphere, communication and birthing experiences.

The visits will seek information from women who have given birth and clinicians/ward staff of all grades involved in care. The process evaluation team will investigate the role of ethnicity and other intersectional socio-demographics in professional, interpersonal and clinician-patient interactions, team dynamics and atmosphere, communication and birthing experiences. They will also observe how variations in practical arrangements, communication and delegation processes and wider structural issues that might affect delivery and experience of maternity care. The site visit will have the following components:

- **Observations of training and PPH management in maternity units**: During the standard care period, PPH training and current clinical practice during scheduled caesarean section and vaginal births will be observed providing a baseline assessment. In the 9-month implementation period and the OBS UK care period: observation of OBS UK training and the care bundle being used in clinical practice will be undertaken to provide a time-sensitive assessment of the process of adoption of the intervention, compliance and sustainability, and how human and organisational factors affect what form this takes. Members of the process evaluation team will be taking field notes using a notepad. They will also hold informal conversations with staff during observations, sections of which may be noted within the de-identified field-notes.
- **In-depth, qualitative interviews with up to 15 members of the specialist and wider team delivering OBS UK**: The national process evaluation team will undertake semi-structured interviews over the course of the standard care, 9-month implementation and OBS UK care periods. The interviews will elicit feedback on the care bundle, including changes required in

relation to individual or organisational capacity to use OBS UK during the trial, but also the longer term. Interviews will be audio recorded and transcribed for analysis. All interviews will be de-identified to enable inclusion of potentially sensitive topics such as team dynamics, allocation of tasks and resources within the team, day-to-day experience of working in a high-pressure environment and the variation in experiences based on demographics such as ethnicity and socioeconomic deprivation. Participants will be invited to reflect also on changes before and after implementation.

- **Qualitative interviews with approximately 4 women (and their birth partners, BP, if interested) in total, per site:** Women who received PPH care and have recovered from the acute episode during pre-implementation, and OBS UK care phases will be identified by a member of the clinical team who will inform the research practitioner at the site. The participants will be selected to represent a range of outcomes (e.g. needed transfusion, ICU admission), ethnicities and ages. Women will be contacted by the research practitioner briefly in the postnatal ward and, if they consent (detailed in Section 9.4), share contact details. They will be contacted for a telephone interview or online with a member of the process evaluation team at a convenient time of their choosing. The interviews may be translated (if required) and will be audio recorded and transcribed for analysis.

	Pre-OBS UK study*	Standard care	Implementation month								OBS UK care	Follow up
			1	2	3	4	5	6	7	8	9	
Advertise site participation in study		x	x	x	x	x	x	x	x	x	x	x	
Targeted source data collection		x	x	x	x	x	x	x	x	x	x	x	
Request NHS digital data linkage		x										x	
Site context questionnaire		x											
Advertise implementation			x	x									
Cascade training			x	x	x	x	x	x	x	x	x	x	
Receive coagulation device and fibrinogen concentrate			x	x	x	x							
Rollout of coagulation device training			x	x	x	x	x	x	x	x	x	x	

Audit and case note reviews			x			x			x			x	
Present audit/case note review data			x	x		x	x		x	x			
Meet with the national QI team			x	x		x			x		x		
QI data reporting- aggregate monthly run charts and aggregate audit/case note review results			x	x	x	x	x	x	x	x	x		
OBS E-Fib and OBS M-Fib data collection including additional research plasma sample collection points for the M-Fib study		X	x	x	x	x	x	x	x	x	x		
Online staff survey											x		
Process evaluation: ethnographic observations, staff and patient interviews	X□	$x^{\dagger}$	$x^{\dagger}$									$x^{\dagger}$	
Psychological questionnaires for women and partners (BP) who experience PPH >1L		$x^{\dagger\dagger}$										$x^{\dagger\dagger}$	$x^{\dagger\dagger}$
Mental health semi-structured interviews													$X^{\dagger\dagger\dagger}$
Cost effectiveness questionnaires for women and partners (EP) who experience PPH >1L		$x^{\dagger\dagger}$										$x^{\dagger\dagger}$	$x^{\dagger\dagger}$
Cost effectiveness questionnaires for women and partners (EP) who do not experience PPH		$x^{\dagger\dagger}$										$x^{\dagger\dagger}$	$x^{\dagger\dagger}$

*4 Welsh sites X□4 Welsh sites including 5-6 staff interviews, 2-3 patient interviews (and birth partners, if appropriate), per site † 1 OBS UK site per sequence including interviews with approximately 4 women (and birth partners, if appropriate) per site , and 12-15 staff per site (up to 90 in total) †† up to 23 women and partners recruited during standard care and up to 23 women and partners recruited during OBS UK care from the 6 sites in sequences 2-5. ††† minimum of 10 women with PTSD symptoms, 10 women with no PTSD symptoms, 10 partners with PTSD symptoms and 10 partners with no PTSD symptoms following completion of the 6 month psychological questionnaire.

Table 1. Summary of trial procedures and data collection

12.6 OBS E-Fib and OBS M-Fib

OBS E-Fib

The OBS E-Fib sub-study requires no intervention and will record routinely collected data.

The following data will be collected for the first 40 eligible cases receiving standard care within the OBS UK trial and the first 40 eligible cases receiving OBS UK care. After 40 cases, with complete data in each phase have been collected, recruitment will stop in that phase.

For a case to be considered to have complete data there will need be a pre-infusion Clauss fibrinogen taken within 120 minutes before the coagulation blood product infusion (FFP, cryoprecipitate or fibrinogen concentrate) and a post-infusion Clauss fibrinogen sample taken within one hour of the infusion ending and before any further coagulation blood products have been given. The dose of FFP, cryoprecipitate or fibrinogen concentrate must be known.

In addition to target source data, the following will be collected:

- Participant booking weight and height
- All haemoglobin, platelet and coagulation (laboratory and VHA) tests immediately before and during the bleeding episode
- All coagulation blood products infused during the bleeding episode (time and dose of infusion and volume of blood loss at the time of infusion)

The primary outcome of the OBS E-Fib sub-study will be to compare the proportion of women with fibrinogen levels ≤2g/L who achieve fibrinogen levels >2g/L after the first cycle of blood coagulation

product transfusion between empirical blood coagulation product (standard, usual UK treatment) and concentrated fibrinogen transfusion (OBS UK treatment).

Additional outcomes will include:

- Increment in fibrinogen after the first cycle of blood coagulation product infusion.
    - This will be calculated as Clauss fibrinogen after the infusion minus Clauss fibrinogen before the infusion in g/L.
- In vivo recovery of Clauss fibrinogen after the first cycle of blood coagulation product transfusion.
    - This will be calculated as the observed increment (calculated as above) in g/L divided by amount of fibrinogen infused/kg booking body weight in g/kg.
- Increment in fibrinogen level and in vivo recovery after second and subsequent cycles of blood coagulation product transfusion in women with fibrinogen ≤2g/L during PPH resuscitation with empirical coagulation product (standard, usual UK treatment) versus concentrated fibrinogen transfusion (OBS UK treatment).
- Blood loss after diagnosis of fibrinogen ≤2g/L during PPH resuscitation with empirical blood coagulation product (standard, usual UK treatment) versus concentrated fibrinogen transfusion (OBS UK treatment).
- Increment and in vivo recovery measured by Rotem Fibtem A5 or TEG CFF during OBS UK care.
- Increment and in vivo recovery will be compared between
    - Standard care and OBS UK care
    - FFP, cryoprecipitate and fibrinogen concentrate
    - Subjects assumed to have AOC and those assumed not to have AOC
        - AOC will be defined as at least one Clauss <2 g/L associated with either a blood loss less than 2500 mL at the time the sample was taken or D-dimer >20000 ng/mL at any time during the bleed.
- The time taken from diagnosis of Clauss fibrinogen <2 g/L to achieving a Clauss fibrinogen >2 g/L will be compared between FFP, cryoprecipitate and fibrinogen concentrate.

OBS M-Fib

In maternity units participating in OBS M-Fib, women or birthing people with obstetric bleeding will receive the OBS UK care bundle. In addition to routine clinical care blood samples, extra research double-spun plasma samples (5-10mL) will be taken by the clinical team providing care at every routine blood sampling episode that occurs during a bleeding episode. The research samples will be labelled with the time of collection and contemporaneous measured blood loss and will be retained on delivery suite until the bleeding has stopped. It is not possible to predict at the onset of bleeding whether a woman will require blood coagulation products for PPH. Therefore, whenever blood tests are taken as part of routine care during a PPH, extra research samples will be taken. As this is at the same time as routine blood sampling, this will not require any additional venepuncture for the woman.

Frequency of sampling will follow the OBS UK PPH care bundle (i.e. if blood loss reaches 1L with bleeding ongoing or if clinical concern of concealed bleeding or coagulopathy and repeated after each 500mL additional blood loss, after infusion of fibrinogen concentrate, cryoprecipitate or FFP or at any time for clinical concern). Infusion and dose of FFP, cryoprecipitate or fibrinogen concentrate will be given according to the OBS UK blood product algorithm.

In order to identify samples for extended testing of coagulation, the following screening criteria will be used:

- ROTEM Fibtem A5 results <9mm or TEG Citrated Functional Fibrinogen Maximum Amplitude (CFF MA) <17mm (corresponding to approximate fibrinogen levels $\leq$2g/L) during the bleeding.
- Clauss fibrinogen $\leq$2g/L during the bleeding.
- Infusion of blood coagulation product (FFP, cryoprecipitate or fibrinogen concentrate) during the bleeding.
- $\geq$4 units allogenic red blood cell transfusion during a PPH as this is a marker for massive PPH.

If any of the screening criteria are met, the research samples will be sent to the laboratory for separation and storage of plasma. Processing will consist of double centrifugation and retention of platelet poor plasma in aliquots at -80^{O}C.

If none of the screening criteria are met, any research samples will be discarded by the clinical team. Confirmation of eligibility will be assessed by the research team prior to seeking consent. If the woman is ineligible or declines consent to participate in the OBS M-Fib sub-study any stored study samples will be destroyed.

Patient demographics and pregnancy details will be collected from the clinical notes after written consent has been confirmed. This will align with and complement the OBS UK Trial targeted source data collection for women who receive a blood product transfusion or experience a PPH >1.5L.

1. Additional demographic and obstetric characteristics will include:

    i. Weight and height at booking obstetric appointment
    ii. Smoking status
    iii. Pre-eclampsia
    iv. Augmentation of labour with oxytocin infusion
    v. Time of onset of 1st, 2nd and 3rd stage of labour
    vi. Time of onset, progress and control of bleeding
    vii. Past medical and surgical history

4. Additional haemorrhage characteristics will include:
    i. All haemoglobin, platelet, coagulation (laboratory and VHA), lactate and renal function tests
    ii. Contemporaneous measured blood loss
    iii. Time of infusion for all blood and blood components
    iv. Time of infusion and volume of any crystalloid/colloid infused during the PPH
    v. Time and dose of tranexamic acid
    vi. Transfer to and duration of higher level of care on the obstetric unit
5. Additional neonatal characteristics
    i. Birth weight
    ii. Duration of neonatal unit admission and level of organ support required
    iii. Indications of fetal wellbeing during pregnancy and delivery
    iv. Indicators of neonatal condition at birth and during early neonatal life
    v. Duration of neonatal inpatient stay

The OBS M-Fib sub-study will undertake:

- Comparison between women with and without AOC including: demographic, obstetric, fetal/neonatal characteristics and PPH progression.
- Detailed phenotyping of the fibrinolytic system in women with and without AOC defined as plasmin/antiplasmin complexes >40 000 ng/mL.
- Increment in fibrinogen level after first and subsequent cycles of blood coagulation product transfusion in women with fibrinogen ≤2g/L during PPH resuscitation with and without AOC defined plasmin/antiplasmin complexes >40 000 ng/mL.
- The role of clear fluid and red blood cell resuscitation in the development of dilutional coagulopathy in PPH.
- Investigation of potential scoring systems to support early diagnosis and treatment of AOC in clinical practice.

12.7 Follow-up

The trial will last 30 months. A subgroup of women and partners who have agreed to participate in the psychology and cost effectiveness sub-studies will be followed up for 6 months after giving birth.

13. Safety reporting

As the components of the care bundle being tested are recommended and used throughout the UK, there are no adverse events which would be anticipated as a unique consequence of participation in the trial. No expedited reporting of adverse events is proposed. We are anticipating that there will be deaths in this trial. However, all of these deaths are expected to be due to other complications of pregnancy or a consequence of the PPH. It is possible that there may be a difference in the rate of maternal death and/or intensive care admission between standard obstetric haemorrhage care and the OBS UK intervention if the latter reduces these outcomes. However, this will not be detected by expedited reporting because (i) the proportion of deaths due to obstetric haemorrhage will be small compared to the background risk of death and differences will be difficult, if not impossible, to detect by reporting of individual deaths, and (ii) this is a cluster randomised trial so adjustment for the clustering will be required to explore whether crude differences in death rates are due to the intervention. Maternal death and ICU admissions will be collected for all participants in the trial and

these outcomes will be monitored by the combined Trial Steering Committee and Independent Data Monitoring and Ethics Committee.

If a woman or birthing person receiving Riastap has an adverse drug reaction (ADR), the MHRA will be informed using the Yellow Card scheme and CSL Behring will be informed via email PhVUK@cslbehring.com as per usual clinical practice within the NHS. These ADRs will not be reported as adverse events to the OBS UK trial team at Cardiff University. ADRs will be reported directly from the participating NHS sites.

13.1 Contraception and pregnancy

13.1.1 Contraception

Not applicable to the study.

13.1.2 Pregnancy reporting whilst participating in the trial

Not applicable to the study.

13.2 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, CI or PI may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14. Statistical considerations

14.1 Randomisation

Maternity units will be randomised to one of six sequences before the start of the study. The size of the maternity unit (births per annum) will be included as a balancing measure. In addition, half the sites in each sequence will be allocated to use the ROTEM point-of-care coagulation device and half to use the TEG point-of-care device, see section 9.5.2.

Randomisation of sites into sequences will be outlined by the study statistician with details of the computer based randomisation process specified in a separate randomisation plan.

14.2 Blinding

The study will not be blinded.

14.3 Sample size

OBS UK primary endpoint

The anticipated reduction in red blood cell transfusion from 27.5 to 18.0 per 1000 maternities is based on the effect size seen in the OBS Cymru pilot study and recently published UK PPH transfusion rates.[5, 22] The average unit size was anticipated to be about 3000 births/year. [42] A stepped wedge cluster RCT with 6 sequences and an estimated average of 750 maternities per 3 month period/unit, requires 5 units to be randomised to each sequence. The total of 30 units gives 93% power to detect the above effect size, based on a two-sided type I error rate of 5% and assuming a "discrete-time decay" correlation structure with intra-class correlation 0.002 (based on previous audit data and similar studies), [43] and cluster auto-correlation 0.80. [44] One additional unit per sequence will be randomised (total of 36 units) to account for potential drop-out, corresponding to a total of 189,000 maternities over 30 months. 189,000 is a conservative estimate based on an assumed average of 3000 maternities per year. All potential sites will be confirmed as ready to start data collection at the same time.

With data from implementation months 5-9 included in the analysis model we will have 90% power to detect a reduction in the primary outcome from 27.5 to 22.0 red blood cell transfusions per 1000 maternities, leaving all other assumptions unchanged. If we 'down-weight' the data from months 5-9 either uniformly (i.e. assign weights of 0.5 for months 5-9) or gradually increasing (i.e. assign weights of 0.2, 0.4, 0.6, 0.8, 1.0 for months 5, 6, 7, 8, 9), reflecting the fact that implementation may not be fully completed during these months, then the minimum effect detectable with 90% power is a reduction from 27.5 to 21.3 red blood cell transfusions per 1000 maternities.

Psychology and cost effectiveness sub-study

For the sample size to maintain power of 80-90% in the sub studies we have allowed for a 75% attrition rate (based on current observation) included additional pre-implementation recruitment from sequence 6 sites and post-implementation from sequence 1 sites and allowed for the observed

deferred pre-implementation recruitment from some sites. Due to practical reasons (study end date) we are not able to recruit people post implementation from sequence 6 sites. This means we will now collect data from 30 sites at pre-implementation (seq 2-6) and 30 sites post implementation (seq 1-5). The sample size calculation is based on recruitment of women/BP experiencing PPH and requires n = 40 women and n = 40 partners to be recruited per site over a 6 month period pre-implementation and the same number again post-implementation (allowing for 75% attrition), with reduced targets for sites with reduced recruitment periods. This will provide ≥80% power for a medium effect size based on a two-sided alpha of 5% and assuming an approximate normal distribution of the outcome data. Sites will also need to recruit a comparator group of non PPH women n=40 and partners n=40 for the cost-effectiveness study. This gives a total of n=1080 PPH women, n= 1080 PPH BP, n=1080 non PPH women, n=1080 partners pre-implementation and the same post-implementation.

The same women and partners will be recruited for both sub-studies, although only BP will be eligible for the psychology study and EP for the cost effectiveness study. In addition, the cost effectiveness study will recruit up to 40+40 women and partners (EP) before the intervention and up to 40+40 women and partners (EP) after the intervention, from 30 sites across sequences 1-6, who did not experience a PPH.

Mental health study

We will interview:

1. A minimum of 10 women/birthing people who reported high levels of PTSD at 6 months (assessed as a score of 33 or more via the Impact of Event Scale-Revised or the top scoring 25% of study sample).
2. A minimum of 10 women/birthing people who reported low levels of PTSD symptoms at 6 months (assessed as a score of 22 or less via the Impact of Event Scale-Revised or the lowest scoring 25% of the study sample).
3. A minimum of 10 birth partners who reported high levels of PTSD symptoms at 6 months (assessed as a score of 33 or more via the Impact of Event Scale-Revised or the top scoring 25% of study sample).

4. A minimum of 10 birth partners who reported low levels of PTSD symptoms at 6 months (assessed as a score of 22 or less via the Impact of Event Scale-Revised or the lowest scoring 25% of the study sample).

Process evaluation

The process evaluation has a number of parts, and includes ethnographic site observations for 3-4 days during the different phases of the OBS UK study. Case studies in four sites that were part of the pilot study (OBS Cymru) will also recruit 5-6 members of staff and 2-3 women who have experienced a PPH of more than 1L for in-depth qualitative interviews. Prospective case studies in 6 sites, one per sequence, will include interviews with 12-15 members of the maternity team and approximately 4 women and partners (BP) who have experienced a PPH of more than 1L (selected from across the three phases).

OBS E-Fib and M-Fib sub-studies

E-Fib (Empiric vs. targeted fibrinogen replacement): Based on data from our recent publication and theoretical modelling of fibrinogen and FFP transfusion in obstetrics,[33,34] we anticipate that the proportion of women with fibrinogen level $\leq$2g/L during obstetric haemorrhage who achieve a fibrinogen level of >2g/L after the first cycle of coagulation product transfusion will increase from 30% after empirical blood coagulation product (standard, usual UK treatment) to 70% after concentrated fibrinogen transfusion (OBS UK treatment). To detect an effect of this magnitude with 90% power whilst controlling a two-sided 5% type I error rate, a sample of 62 women is required (calculation approximated based on a chi-squared test). To account for up to 20% of missing data (e.g. due to blood samples being unusable for laboratory analysis), the sample size target is inflated to 80 women (40 receiving standard, usual treatment and 40 OBS UK treatment).

A requirement for inclusion is the availability of laboratory coagulation tests taken before and after the first cycle of blood product transfusion. This is unlikely to be available for all cases. We plan to recruit from maternity units providing care to around 80,000 women over 2 years. Based on an anticipated coagulopathy rate (fibrinogen <2g/L) of about 3 per 1000 maternities,[33] we expect approximately 120 per 40,000 women to have coagulopathy during a PPH. The first 40 consecutive

eligible women receiving the standard, usual treatment and the first 40 consecutive eligible women receiving and OBS UK care, will be included in the OBS E-Fib study.

M-Fib (Mechanisms) sub-study

110 women fulfilling inclusion criteria for extended testing of coagulation during PPH resuscitation. Some of these women may also participate in OBS E-Fib- see figure 3 and 4.

- 80 women with coagulopathy and at least one stored study sample (as defined in section 8.1).
- It is anticipated that around half will have dilutional coagulopathy and half AOC based on our previous studies. 30 women with no coagulopathy (as defined in section 8.1) but transfused at least 4 units of red blood cells during PPH.

Based on our previous hypothesis generating study and the heterogeneity of coagulation results, we anticipate in OBS UK treatment around 1-2 per 1000 maternities will develop AOC and around 1-2 per 1000 a dilutional coagulopathy. In addition, approximately 0.3 per 1000 maternities will receive ≥4 units RBC transfusion without development of coagulopathy.

In the M-Fib sub-study we plan to recruit from 6 maternity units providing OBS UK treatment to around 30,000 women for 2 years. This will be a total of 60,000 maternities. We anticipate that around 180 will develop a coagulopathy.

The sample size is based on a realistic number of cases that can be recruited from the sites within the time period. The number of sites is based on sites within OBS UK that have the capacity to process and store research samples outside of routine working hours. No specific hypothesis is being tested and so no calculation is appropriate.

In addition, healthy women with uncomplicated pregnancies who are not bleeding will be recruited as controls (60 women):

- 30 women before and one hour after an uncomplicated planned caesarean birth

- 30 women during established uncomplicated labour but who are not pushing and one hour after uncomplicated vaginal birth

14.4 Missing, unused & spurious data

Details will be provided in the Statistical Analysis Plan (SAP).

14.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the trial

There will be two stop/go points which are assessed at a maternity unit level:

- 9 months: 30 sites with signed contracts with Cardiff University
- 24 months: 75% of sites will have provided all the primary outcome data from the first 3 months of the study

14.7 Inclusion in analysis

All women giving birth at the (up to) 36 maternity units included in the study during the data collection periods (pre- and post- implementation of the OBS UK intervention, and months 5-9 of the implementation period) will be included in the analysis of the main study outcomes unless data opt-out registration has been completed. The details of the sub-studies are detailed in Sections 12.

15. Analysis

15.1 Main analysis

A full statistical analysis plan will be agreed prior to the end of the study. The characteristics of women in participating obstetric units as well as characteristics of the units themselves will be summarised descriptively and graphically by exposure status (OBS UK care or standard care), cluster/sequence and time period. Aggregate data on ethnicity and socioeconomic factors will be collected.

The primary analysis will be intention-to-treat (women will be analysed as receiving control or intervention according to the randomisation status of their obstetric unit, regardless of adherence to the intervention) and use a logistic mixed-effects regression model with random cluster effects, fixed effects for time period (to capture secular trends) and exposure status as well as fixed effects for the stratification variables (unit size) to estimate the odds ratio of receiving red blood cell transfusion for PPH between the OBS UK care and standard care. The intervention effect will be presented as a point estimate with a two-sided 95% confidence interval (CI) and p-value. If the estimate favours the OBS UK care and the 95% CI excludes one, effectiveness of the intervention at the 5% level will be concluded.

Sensitivity analyses will model an autoregressive correlation structure, secular trends that differ between (randomised groups of) units and intervention effect heterogeneity across time and/or (randomised groups of) units.[45, 46] In a further sensitivity analysis a marginal mean model will be fitted using generalised estimating equations with robust standard errors instead of mixed-effects regression, allowing a more population-focused interpretation. [47] In yet another sensitivity analysis will exclude or 'down-weight' the data collected during months 5-9 of the implementation period.

Complexity relating to partial adoption of the care bundle: If some units implement individual elements of the OBS care bundle prior to entering the 9-month implementation period, or if individual units fail to implement the intervention during the 9-month period, this will be modelled in a separate sensitivity analysis. No unit will have adopted the point-of-care tests of coagulation or used QI methods for implementation of the entire OBS UK care bundle prior to the 9-month implementation period. The variation in prior adoption and or partial implementation of individual elements will also be measured and considered in the process evaluation.

Reporting of results will follow the recommendations in the relevant CONSORT extension.[48] A detailed analysis plan will be finalised and signed off prior to database lock.

Minimising bias: Since the intervention will be delivered at a maternity unit level and individual consent will not be required for the primary outcome, selection bias will not affect data collection.

15.1.1 Sub-group & interim analysis

No formal interim analyses are planned. Subgroup analyses will explore the impact of ethnicity (proportion of minority mothers and/or staff) and other aspects of demographic diversity on the intervention effect, by adding interaction terms with intervention to the analysis model. Similar analyses will be performed for the secondary clinical and psychological outcomes with linear instead of logistic models used for continuous outcomes for which at least approximate normality can be assumed.

15.2 Process Evaluation analysis

The process evaluation will be strongly guided by the concerns raised by MBRRACE regarding inequalities in maternity outcomes based on socio-demographics and by the principles of equality, diversity and inclusion (EDI), and we will enrol theory to help us investigate all of these issues. We will employ a combination of Normalisation Process Theory (NPT) and the Consolidation Framework for Implementation Research (CFIR) to analyse our data. Currently neither frameworks attend explicitly to intersectionality or EDI concerns but we will develop these theories in this regard. The process evaluation will consider EDI in many stages including:

1. The Wales based site visits which will allow preliminary exploration of the intersection between ethnicity and socioeconomic deprivation in the delivery and impact of the OBS Cymru intervention for both patients, partners if they would like to be involved, and staff. Although we acknowledge that there is a high proportion of White British women in Wales, compared to the rest of the UK, there is also substantial variation in socioeconomic deprivation. These data will be used to inform the prospective case studies.
2. The surveys which will describe site context and include measurement of demographic variables for staff and patient populations. Thus, we will examine, right from the start of the study, how the demography of maternity staff (temporary and permanent) and patients is related to the (pre-trial) staffing levels, training and support offered and clinical risk management processes including management of PPH.

3. We will also analyse the demographic profiles of the multi-professional teams and champions who complete the evaluation survey at the end of the implementation period, paying special attention to sites that have performed well in the study and those that have not, to see if/how the intersectional

identities within each team affect their responses to the experience of the study.

4. We will explore relationships between adoption of the OBS UK care bundle (e.g. via the audits and case note reviews) and population EDI. We will also investigate how the QI methods employed respond to demographic concerns, for example, how do they deal with communication challenges when there are language barriers? We will explore the training and education materials in relation to diversity, for example in the use of language and cultural or religious sensitivities regarding childbirth and blood loss.

5. The 6 case studies will provide an opportunity to interrogate closely how composition of staff teams, site location, patient profiles, staffing levels etc affect issues around access, provision and experience of care and communication during all 3 phases of the study (pre-implementation, implementation and OBS UK stages). Site observations of training and PPH management will be useful in assessing how the training is taking place in obstetric units and how it is received and understood by different members of the teams performing different roles. The qualitative interviews with members of the team (both recorded interviews and informal conversations) will allow further examination of sensitive topics around team dynamics and how intersectional identities and positionalities with respect to each other affect allocation of tasks and resources, day-to-day working and access to senior clinicians during emergencies. Qualitative interviews with approximately 4 women (and possibly also their birth partners) per site who will be purposively selected for maximum variation in terms of EDI will also allow exploration of the impact of literacy disadvantage or multiple health problems, or other structural disadvantages linked to poverty or disability.

The QI support and activity will be another focus for evaluation. The process evaluation will run throughout the study to follow and understand the implementation journey. For example, we want to understand potential variation in how the QI activities 'work' in different local contexts. The prospective case studies in 6 units will thus be chosen for maximum variation in service configuration, geography, deprivation and ethnic composition of staff and patients. In addition, QI data for all sites will also be recorded (eg. training sessions, uptake of measurement of blood loss). These data and the prospective case studies will inform the statistical analysis to understand how variation in uptake of the care bundle impacts on primary and secondary outcomes.

15.3 Economic evaluation

A bivariate multi-level model that accounts for time, clustering and correlation between costs and outcomes, with multiple imputation of missing data, will be constructed to generate within-trial estimates of incremental cost-effectiveness associated with the intervention. For the within-trial health economic evaluation (HEE), cost-effectiveness will be expressed as incremental cost per confirmed case of red blood cell transfusion avoided. Sensitivity analyses will assess the impact of uncertainty surrounding components of the HEE. Sensitivity analyses will include re-estimation of cost-effectiveness based on cases with complete data. Separate decision-analytic modelling will extrapolate the time horizon of the HEE and express cost-effectiveness in terms of incremental cost per quality-adjusted life year (QALY) gained over a lifetime horizon. This will draw upon estimates of economic outcomes (health and social care resource use, economic costs borne by women/ carers and EQ-5D-5L health-related quality of life outcomes) provided by women completing questionnaires at 6 weeks and 6 months postpartum, supplemented with data for model parameter inputs identified through targeted literature searches and HES data. Estimates will be considered over an extended time horizon, since complications such as blood transfusion, hysterectomy and PTSD potentially have longer term impacts. Multi-parameter uncertainty in the decision-analytic model will be addressed using probabilistic sensitivity analysis. Cost-effectiveness acceptability curves will be used to show the probability of cost- effectiveness of the intervention at alternative cost-effectiveness thresholds. The HEE will be prospectively planned and detailed within a 'Health Economic Analysis Plan' signed off by the Trial Steering Committee.

15.4 OBS E-Fib and OBS M-Fib sub-studies

Normal ranges of demographic, obstetric, PPH and neonatal characteristics will be presented using descriptive statistics. Outliers will be identified with reference to the range in healthy pregnant controls and in women with PPH but no coagulopathy identified in our recent study.[51] Differences between groups will be analysed using appropriate tests and confidence interval procedures. The OBS E and M Fib analyses will be pre-specified in a subsection of the main OBS UK Trial statistical analysis plan.

OBS E-Fib sub-study

We will use a logistic regression model to estimate the effect of targeted concentrated fibrinogen resuscitation (OBS UK treatment) of coagulopathy during PPH resuscitation as compared to empirical blood coagulation product transfusion (standard, usual treatment) on the proportion of women with fibrinogen levels ≤2g/L who achieve levels >2g/L after the first cycle of blood coagulation product transfusion. The analysis will adjust for important confounders by including them as fixed effects in the regression model, and for clustering, by including random effects for maternity units. The estimated odds ratio will be presented alongside a 95% confidence interval.

The effect of FFP/fibrinogen concentrate/cryoprecipitate infusion on coagulation parameters will be reported. Specifically, for fibrinogen, the increment will be the increase in Clauss and antigenic fibrinogen (for those cases also in the OBS M-Fib sub-study) measured in g/L per g/kg infused. This will be described according to the aetiology of the bleed.

OBS M-Fib sub-study

Coagulopathies will be categorised including the degree of hyperfibrinolysis and/or hypo-dysfibrinogenaemia. Markers of coagulation will be compared between healthy pregnant controls and women with PPH subcategorised into those with and without AOC. Thresholds and different diagnostic criteria for AOC and dilutional coagulopathy will be explored, including PAP >40,000ng/ml at any time. The effect of any FFP/fibrinogen concentrate/cryoprecipitate infusion on coagulation parameters throughout the PPH will be reported according to the nature of the coagulopathy.

Risk factors for AOC and dilutional coagulopathy will be identified using logistic regression to inform the derivation of a clinically useful risk score which may be useful to identify the type of coagulopathy at the bedside. The ability to fully validate such a score as part of this study will however be limited given the lack of an independent validation cohort.

16. Data Management

16.1 Data collection

16.1.1 Aggregate primary outcome data

Aggregate primary outcome data collected from both maternity and blood bank databases will be entered by the research practitioner into the OBS UK Trial database.

16.1.2 Targeted source data and routine NHS data sources

A section 251 approval from the Confidentiality Advisory Group (CAG) in England, Public Benefit and Privacy Panel for Health (PBPP) in Scotland will be sought to retrieve routinely collected data from NHS databases and targeted source data without individual consent for the OBS UK trial. Using unique patient identifiers, the routine national NHS data will be linked to specific target source data., NHS England will manage the linkage for the cohort in England and the Electronic Data Research and Innovation Services (eDRIS) will manage the linkage for the cohort in Scotland. Both linked national data sets will be made available in the National Safe Haven (NSH) in Scotland, an accredited Trusted Research Environment (TRE) negating the risk of individuals being identified in the analysis of the linked data sets. Sites in Northern Ireland will collect pseudonymised targeted source data and no routine data will be obtained.

16.1.3 Targeted source data

Targeted source data will be extracted from local sources by the local research practitioner. In England, on creation of the record in the OBS UK Trial database they will be assigned a trial identity code number. Patient identifiers (NHS number, postcode, date of birth) will be used to enable linkage with NHS routine data sources. Access to the online OBS UK Trial database will be limited to site staff, named research practitioners and CTU staff via personal usernames and passwords. Access will be granted and managed by the CTU trial management team. Routinely collected NHS England data will be linked to the targeted source data extracted from the OBS UK Trial database using an established method for managing and linking data in an anonymised manner within NHS England's own secure environment. NHS England will receive the OBS UK trial database dataset with a list of corresponding study IDs (stored within an encrypted password protected files) for each site in

England from the Cardiff University trial team, participant identifiers will be replaced from the trial data with corresponding OBS UK study IDs. After linkage and de-identification occurs, NHS England will securely transfer the anonymised dataset to NSH (TRE), only approved trained trial team members will be able to access this dataset via a secure portal to complete trial analyses. The trial team members with approved access to NSH will not be able to identify any individual within the dataset, this satisfies the data provider's (NHS England) requirements of confidentiality and anonymity. Non-approved trial team members will be unable to access the portal / dataset in NSH at any point within the trial.

In order to avoid including women who have opted out of data collection through the national data opt service in England, sites will use the NHS MESH (Message Exchange for Social Care and Health) service to provide a list of the relevant NHS numbers to be checked against the national data opt-out repository. The site will receive a list of NHS numbers for the records that cannot be disclosed for the targeted data collection. Site visits for data monitoring cannot be blinded because the intervention is being delivered at a maternity unit level, although data reliability, completeness and compliance with opt out requests will be checked. Inconsistencies between local and national data capture will be reported.

Sites in Northern Ireland will enter pseudonymised targeted source data and no patient identifiers will be recorded in the OBS UK database.

There is no national opt-out in Scotland and so anonymised data will be provided by the sites for women who have a PPH of >1.5L and/or receive a blood transfusion for PPH. The only personal data collected will be the date of birth of the baby. PBPP approval will be sought to link this data to routinely collected dataset in Scotland. This will be facilitated by sites maintaining a spreadsheet of Study IDs and the corresponding CHI number, which will be provided to NHS Scotland at the time of the linkage.

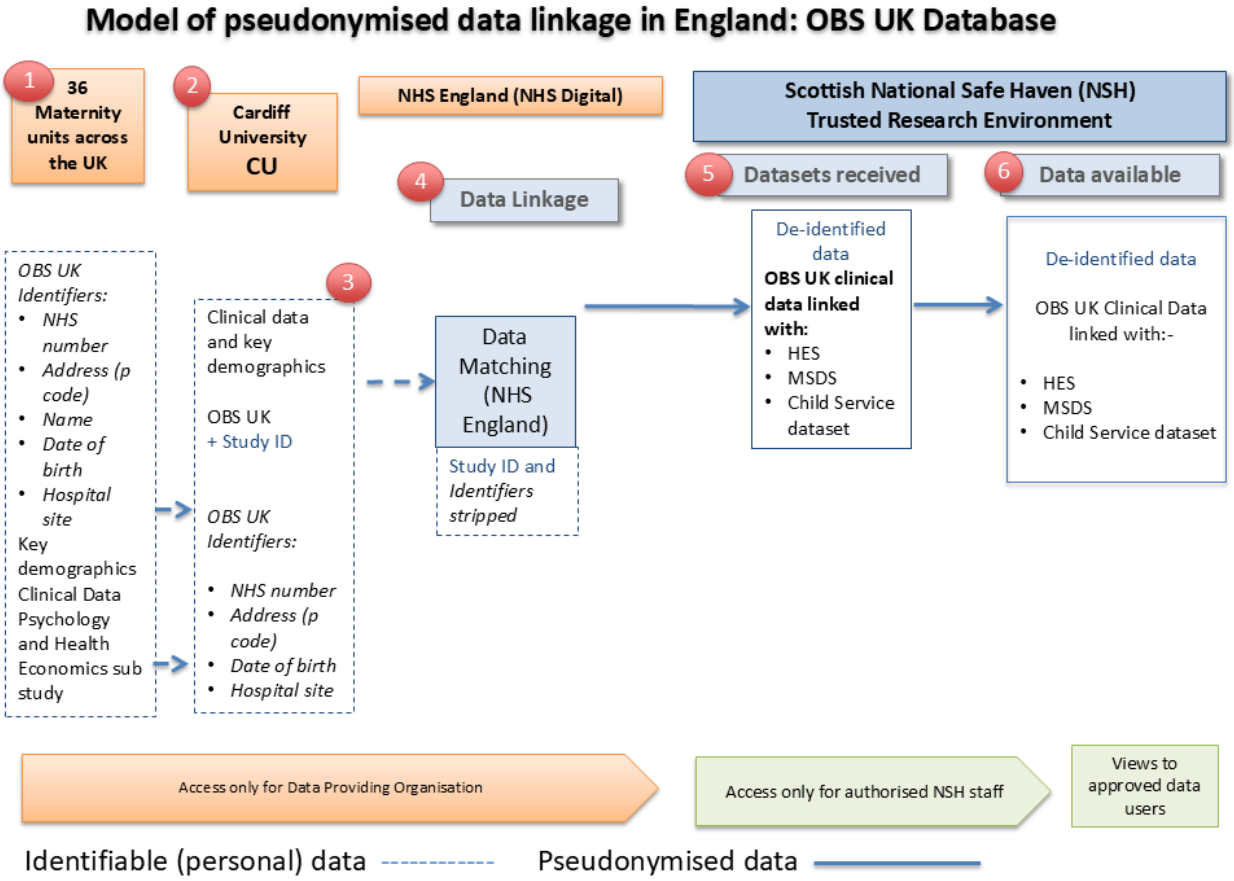
16.1.4 Routine NHS data sources

The routine NHS data sources which will be used for the OBS UK trial include relevant datasets from England and Scotland such as the Hospital Episode Statistics, Maternity Services Dataset, Children and Young People's Health Services Dataset, Child Health Surveillance System. We have one site in Northern Ireland, however currently it is not possible to access routinely collected NHS data as it is

from England and Scotland. If this situation changes during the course of the study, we will make an application to request access.

16.2 Linkage of targeted source data with national datasets

The process for linking clinical data held by Cardiff University in the OBS UK Trial database using the Anonymised Linking Field (ALF) file to national NHS datasets (NHS England and The electronic Data Research and Innovation Service (eDRIS)) is illustrated in the data flow charts. This follows an established secure method for pseudo-anonymised data linkage. The resulting dataset will be safely stored in the TRE, managed by eDRIS. All data cleaning and analyses will be carried out via the NSH remote portal by the study data manager(s), statistician and health economist. See Figure 8 for England and figure 9 for Scotland. Sites in Northern Ireland will enter pseudonymised targeted source data. No patient identifiers will be recorded in the OBS UK database and no linkage will be performed.



Model of pseudonymised data linkage: OBS UK Database

1) Data from the hospital sites in England will be collected by the research midwife at site for women who have had a PPH >1.5l and or a blood transfusion entered onto the OBS UK trial database held at Cardiff University.

2) At Cardiff University identifiable data and clinical data will be held separately. Each individual will be assigned a study identifier (ID) that uniquely identifies them. This will be used to link the two datasets together. Individuals will be from sites in England.

3) Identifiable data from OBS UK participants for women who have had a PPH >1.5l and or a blood transfusion will be sent to NHS England (NHS Digital) (sites in England).

4) NHS England (NHS Digital) will match these individuals to the data that they hold in the Hospital Episode Statistics (HES), Maternity Services Data Set (MSDS) and the Community Services datasets (CSDS) (England). All clinical records of study participants and their babies, within the time frame requested, from the HES, MSDS and CSDS datasets (sites in England) will be sent to the National Safe Haven (NSH) in University of Edinburgh, Scotland, managed by eDRIS. Identifiable data will be removed before sending to NSH.

5) The data are received by eDRIS and loaded into the NSH server.

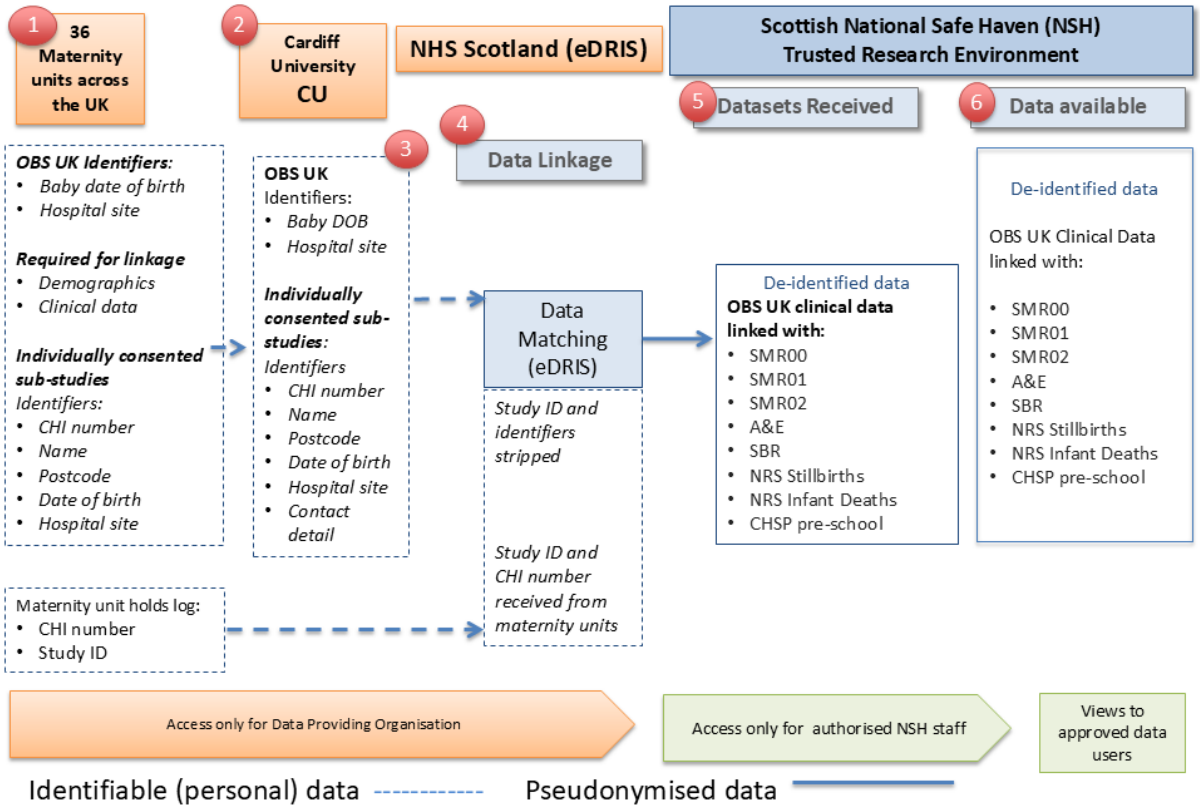
6) A project specific data view is created and approved data users at Cardiff University can access this remotely using a University owned device via a virtual private network (VPN). Data cannot be removed or transferred unless authorised by NSH.

Data users are subject to:
- An approved data access application (via PBPP and eDRIS)
- Data user verification
- Data access agreement (NSH)
- Physical & procedural controls (approved by NHS England, NHS Scotland and NSH)

OBS UK DATA LINKAGE ENG_05MAR25_v2.0

Figure 8. Data Flow Chart for England

Model of pseudonymised data linkage in Scotland: OBS UK Database



Model of pseudonymised data linkage: OBS UK Database

1) Data from hospitals sites in Scotland will be collected by the research midwife at site for women who have had a PPH >1.5l and or a blood transfusion entered on to the OBS UK trial database held at Cardiff University. Some identifiers will be sent to Cardiff University, and CHI number and Study ID will be sent directly to eDRIS from participating maternity units.

2) At Cardiff University identifiable data and clinical data will be held separately. Each individual will be assigned a study identifier (ID) that uniquely identifies them. This will be used to link the two datasets together. Individuals will be from sites in Scotland.

3) Identifiable data from OBS UK participants for women who have had a PPH >1.5l and or a blood transfusion will be sent to NHS Scotland (eDRIS) (sites in Scotland).

4) eDRIS will match these individuals to the data that they hold in SMR00, SMR01, SMR02, A&E, SBR, NRS Stillbirths, NRS Infant Deaths, CHSP pre-school. All clinical records of study participants and their babies, within the time frame requested, from the SMR00, SMR01, SMR02, A&E, SBR, NRS Stillbirths, NRS Infant Deaths, CHSP pre-school datasets will be sent to NSH. Identifiable data will be stripped before sending to NSH.

5) The data are made available by eDRIS and loaded into the NSH server.

6) A project specific data view is created and approved data users at Cardiff University can access this remotely using a University owned device via a virtual private network (VPN). Data cannot be removed or transferred unless authorised by NSH.

Data users are subject to:
- An approved data access application (via PBPP and eDRIS)
- Data user verification
- Data access agreement (NSH)
- Physical & procedural controls (approved by NHS England, NHS Scotland and NSH)

OBS UK DATA LINKAGE SCOT_05MAR25_v2.0

Figure 9. Data Flow Chart for Scotland

16.3 Completion of CRFs

16.3.1 Paper CRFs

Data for the psychological and economic sub-studies may be collect online, via paper CRF or over the telephone with the local research practitioner.

16.3.2 Electronic CRFs

Data will be recorded using as a web-based system. This is a secure encrypted system accessed by an institutional password, in compliance with the Data Protection Act 2018. The system can be accessed on:

https://redcap.ctr.cardiff.ac.uk/redcap/redcap_v13.7.5/index.php?pid=307

A user password will be supplied to investigators upon completion of all processes required prior to opening.

The CRF should be returned updated every month. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the electronic CRF.

CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to

respond to the data query on the data clarification form. The case report form pages should not be altered.

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification e-form should be returned to the CTR and a copy retained at the site.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in a timely manner.

Data protection

All trial staff and investigators will endeavour to protect the rights of the trial participants to privacy and to data opt-out, and will adhere to the Data Protection Act, 2018. The routine NHS data requested will only contain the minimum required information for the purposes of the trial and for accurate data linkage. In England linkage variables (mother's NHS number, date of birth and postcode and baby's NHS number) will be obtained for the targeted source data. The coding list that connects the linkage variables to the trial participant identifier will be retained in a separate secure environment with access limited to the data analyst(s) performing the linkage. Clinical data will be stored in a separate location from the identifiable data and in accordance with Cardiff University's and CTR's governance processes. Access to the information will be limited to the trial staff, investigators and relevant regulatory authorities. Data extracted from NHS routine database providers for all women giving birth in maternity units participating in OBS UK will be linked to the target source data by the data providers using an established method for managing and linking data in an anonymised manner via secure environments within NHS England and Scotland (eDRIS) so that the researchers cannot identify any individual in the resulting data set, and to satisfy the requirements of data providers for preservation of confidentiality and anonymity. All patient identifiable data will be removed from the final dataset once the patient data has been linked between the data sets, so that identifiable information will not be included in the datasets for analysis. Electronic data will be stored on the OBS UK Trial Database, Cardiff University and University of Oxford (for the Process Evaluation) servers, accessed via password protected, firewall protected and backed up computers and held in accordance with the data providers' security requirements. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Electronic data held at Cardiff University will be backed up to both local and

remote media in encrypted format. Access to data held in the TRE managed by eDRIS will be limited to specific trial staff who will be undertaking or analysis of data and have undertaken approved training.

At the end of any long-term follow-up, eDRIS will be responsible for destroying the routine data, as per the data providers requirements in accordance with the data sharing agreement requirements set with each data provider. The OBS UK Trial database will be retained after the trial has finished and securely stored as per the requirements of the Sponsor (Cardiff University).

A data management plan will be published prior to sponsor approval for study initiation.

17. Translational research or sub trial

Not applicable

18. Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

19. Patient and Public Involvement

A PPI plan will be published.

Throughout the study we will be utilising the expertise and support of Egality Health. Egality is a community engagement agency, addressing health inequalities by improving inclusion in research. They work with their network of community organisations, connecting the groups most impacted by health inequalities with the health and life sciences sector. Together, they will collaborate to bring new insights, new ways of working, and deliver creative campaigns and strategies, that increase diversity in research and improve health inequalities. Their EDI strategy spans all under-represented groups in health research, including according to ethnicity, gender, disabilities and socio-economic status. While Egality's initial work mainly focused on improving diversity in terms of ethnicity, they are continuing to expand their networks and are connecting with community organisations who work with the queer community, women's health, and disabled people. Organisations already in their network, such as HAREF Connected Voice, have the reach into these communities through its network in the North East.

The trial management committee includes two lay members with personal experience of PPH who will attend the monthly meetings. These two people will chair a PPI focus group which will meet at least every 6 months throughout the study and provide advice to the study team.

20. End of Trial definition

The implementation of the intervention 9-month phase will be followed by an OBS UK care period of between 3 and 18 months, depending on sequences.

The end of the trial is defined as the date of final data capture (final data entry and data retrieval from NHS Digital sources) to meet the trial endpoints. In this case end of trial is defined as up to 3 months after the termination of the OBS UK period for all sites.

The Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

21. Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

22. Regulatory Considerations

22.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site e.g. HCRW if Wales led and HRA if English led.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

22.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance in accordance with the Data Protection Act 2018. The data custodian and the translational sample custodian for this trial is the Dr Sarah Bell. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), and postcode to register and trace participants with the NHS Digital.

22.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.
- Negligent harm: Where studies are carried out in an NHS Trust or Health Board, the NHS Trust or health Board continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

22.4 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial. Please see the delegation log for further information on responsibilities delegated to CTR.

Cardiff University shall be responsible for ensuring that the trial is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- Data Protection Act (2018)
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

22.5 Funding

The study is funded by the National Institute for Health and Care Research.

Funding for the ROTEM devices, including cartridges and technical support, is supplied by Werfen (Barcelona, Spain). A CE marked device being used for purpose.

Funding for the TEG devices, including cartridges and technical support, is supplied by Haemonetics Corporation (Boston, USA). A CE marked device being used for purpose.

Funding for Riastap (fibrinogen concentrate) is provided by CSL Behring for the duration of the implementation and OBS UK care periods. This is not an IMP.

The trial will be adopted on the NIHR portfolio.

23. Trial management

23.1 Project Team (PT)

The Project Team (PT) will meet weekly and will include the PI, Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team

will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

23.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the study. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

23.3 Independent Data Monitoring Committee (IDMC) and Trial steering committee (TSC)

The IDMC will be combined with the TSC into a single oversight committee. In order to monitor accumulating data on safety and any trial intervention benefit, an oversight committee will be established. The Committee will consist of an independent chair and at least three other independent members including a patient representative. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The oversight committee will provide overall supervision for the study and provide advice through its independent chair. The ultimate decision for the continuation of the study lies with the oversight. Committee members will be required to sign up to the remit and conditions as set out in the Charter.

24. Quality Control and Assurance

24.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the OBS UK trial. Moderate monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

24.1.1 Monitoring of aggregate data

All sites will be required to attend 3 monthly monitoring reviews of aggregate and target source data.

24.1.2 Monitoring of trial supplies

Sites will be required to maintain accountability records for the use of TEG/ROTEM cartridges, and RiaSTAP (fibrinogen), and report to the CTR as specified in the monitoring plan.

24.2 Audits & inspections

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents

The study may be audited by NHS Digital Audit Team.

The trial is participant to inspection by NIHR as the regulatory body. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

25. Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. We will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. At the local level, we will interact with and promote the research findings through wider NHS Trusts.

We will ensure the information centre is acknowledged as per the data sharing agreement for any publication using NHS Digital (or other information centre) data.

26. References

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Appendix 1.

Background to E and M-Fib sub-studies

Coagulopathy in obstetric bleeding, affects around 3-5 per 1000 maternities (2000-3500 women a year in the UK).[22,51] It is associated with adverse maternal and fetal outcomes including massive PPH (≥2.5L blood loss), blood transfusion, intensive care unit (ICU) admission, hysterectomy and death.[52-54,35] A competent haemostatic system is required for medical treatments and/or obstetric interventions to be effective in stopping bleeding and therefore is a key component of resuscitation and the prevention of PPH progression.

Research investigating optimal coagulation resuscitation strategies during PPH is minimal when compared to non-pregnant settings such as major trauma. In the absence of research in obstetric settings, evidence has been extrapolated from non-pregnant bleeding studies. National guidance for PPH management in the UK does not mandate use of viscoelastometric haemostatic assays (VHA) and recommends empirical use of fresh frozen plasma (FFP) in the absence of coagulation results.[3] We have previously shown that a fibrinogen level >2g/L is adequate for haemostasis during PPH,[35] and this is a key management target in treating obstetric coagulopathy.[3] However the optimal strategy to achieve this in clinical practice is unknown. Hypofibrinogenaemia (fibrinogen level ≤2 g/L) is found in about 5% of PPH >1500 mL increasing to 17% of PPH >2500mL, whilst derangements of prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count are less common.[11,33] Fibrinogen can be replaced by transfusing FFP or concentrated forms of fibrinogen (either cryoprecipitate or fibrinogen concentrate). The concentration of fibrinogen differs between FFP (about 2.5g/L), cryoprecipitate (about 10g/L) and fibrinogen concentrate (about 20g/L). A theoretical modelling study has indicated that in hypofibrinogenaemia (≤2g/L), FFP is less effective in achieving fibrinogen levels of >2g/L (the therapeutic target) when compared to more concentrated forms of fibrinogen,[34] but no prospective clinical studies have compared the efficacy of different blood products in treatment of acquired hypofibrinogenaemia during obstetric haemorrhage. We hypothesise that fibrinogen replacement using empirical blood coagulation product transfusion will be less effective than point of care guided concentrated fibrinogen in achieving fibrinogen levels >2g/L in women with hypofibrinogenaemia (≤2g/L). This information is urgently required to optimise treatment and provide sufficient evidence to inform national guidelines and will be investigated in the OBS E-Fib study.

We have recently published the results of a single centre prospective observational study of PPH, which was designed to characterise, in detail, obstetric coagulopathy.[51] Coagulopathy was found in around 2.5% of women early during bleeding (first blood testing at around 1000ml blood loss) with the overall incidence around 5%. Two distinct types of coagulopathy were identified:

Dilutional coagulopathy (due to loss and dilution of clotting factors in massive blood loss). At the start of most PPH, maternal coagulation is enhanced from the non-pregnant baseline due to physiological adaptations of pregnancy related to increased levels of clotting factors such as fibrinogen and factor VIII. The common causes of PPH are uterine atony (failure of the uterus to contract after childbirth), trauma to the genital tract or retained products of conception. If the underlying cause is not identified and treated bleeding will continue. As blood loss increases, a linear reduction in clotting factor levels occurs (from the enhanced starting levels) although coagulation is maintained until a critical threshold is reached. Fibrinogen is the first clotting factor to fall to the critical threshold of (≤2g/L) and typically this occurs when there is blood loss of 3L. Other clotting factors usually remain adequate until 4-5L blood loss.

Acute Obstetric Coagulopathy (AOC) (a unique, severe coagulopathy previously undescribed). In contrast to dilutional coagulopathy, which occurred in a predictable manner in relation to blood loss, AOC was found early, or even before bleeding started, and often in association with foetal and/or neonatal death (50%). AOC was defined after post-hoc analysis of the coagulation parameters based on statistically significantly outliers in markers of hyperfibrinolysis (defined as a plasmin/antiplasmin levels >40,000 ng/mL). AOC was characterised by:

a. Massive hyperfibrinolysis leading to clot breakdown
b. Severe hypofibrinogenaemia (<2g/L)
c. Dysfibrinogenaemia (during AOC fibrinogen function was inhibited contributing to very low functional levels of fibrinogen)
d. Disproportionately reduced factor V and factor VIII
e. Increased activated protein C levels.

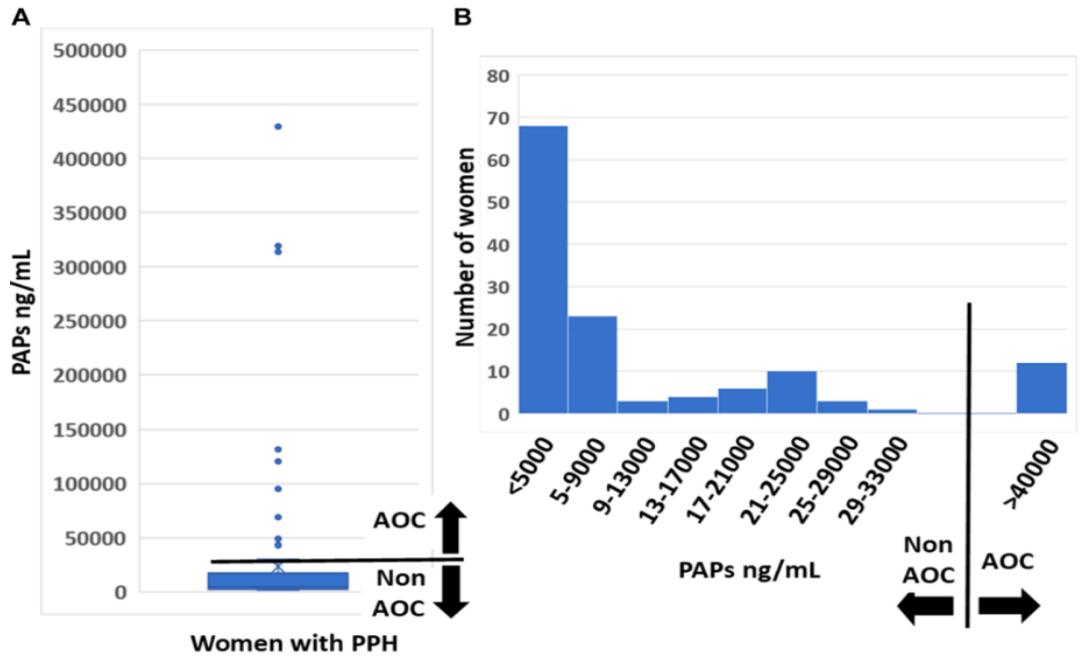

Figure 1 Definition of Acute Obstetric Coagulopathy (AOC).

Plasmin-anti-plasmin complexes (PAPs) are a marker of recent plasmin generation and fibrinolysis. Images A &B illustrate the highest level of PAPs measured in all women with severe PPH (n=130) in the OBS Plus study. The statistical outliers are indicated by the dots in image A, with the very high levels of PAP indicating massive plasmin generation and fibrinolysis. The diagnostic threshold of 40 000 ng/mL, chosen in the study to define AOC in post-hoc analysis of the coagulation data, is indicated by the arrows.

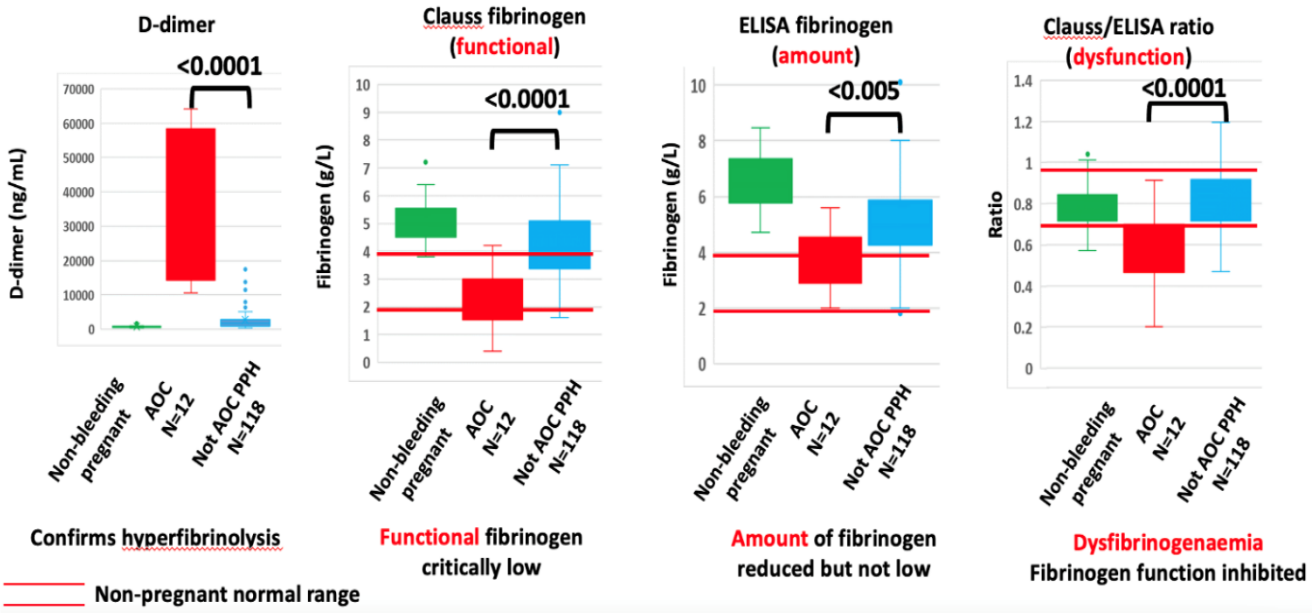

Figure 2 Coagulation changes in Acute Obstetric Coagulopathy (AOC).

Four charts comparing characteristics of healthy, non-bleeding pregnant controls n=37 (green box), women with AOC n=12 (red box) and women with severe PPH without AOC n=118 (blue box). Left to right, the first chart shows D-dimer levels, massive hyperfibrinolysis is shown by the elevated D-dimers in the AOC group. The second chart shows the levels of functional Clauss fibrinogen which are critically low in the AOC group. The third chart shows the amount of fibrinogen measured by the ELISA method, showing the total amount of fibrinogen in the plasma, which is reduced in AOC but not to the same extent as the functional fibrinogen. The fourth chart shows the ratio of functional (Clauss) to total (ELISA) fibrinogen. The low ratio reflects in-vivo inhibition of fibrinogen in the AOC group and is called dysfibrinogenaemia.

Research is required to validate the findings of this hypothesis generating study and further investigate potential mechanisms for AOC. Questions to be addressed include:

a. What causes the hyperfibrinolysis? Is this due to:
    a. Activation via urokinase plasminogen activator, tissue plasminogen activator, kallikrein or other pathways and/or
    b. Dysregulation of inhibition via plasminogen activator inhibitors 1 and 2, $\alpha_2$antiplasmin and/or C1 esterase inhibitor.

b. What is the mechanism of inhibition of fibrinogen function? Is this due to:
    a. Inhibition by fibrin degradation products and/or
    b. Alternative causes (eg. structural changes).
c. Why are factors V and VIII depleted but other coagulation factors preserved? Is this due to:
    a. Cleavage via plasmin or activate protein C and/or
    b. Other mechanisms.
d. What is the effect on clot structure and strength?

Investigation of the nature and mechanism of PPH coagulopathy will improve identification of different coagulopathies and enable targeted treatment to prevent progression of bleeding and optimise effectiveness of obstetric interventions. In our recent study, 50% of all cases of coagulopathy were classified as AOC and 50% as dilutional coagulopathy. Empirical resuscitation with fixed ratios of FFP:RBC transfusion may prevent development of dilutional coagulopathy, but we hypothesise that this approach might be ineffective in the treatment of AOC because of early critically low fibrinogen and fibrinogen inhibition. As there is a strong association of AOC with fetal and neonatal death, understanding mechanisms may ultimately lead to strategies to improve fetal and maternal outcomes in this poorly understood area. The type, incidence and mechanisms of PPH coagulopathy will be investigated in the Mechanisms study (OBS M-Fib).

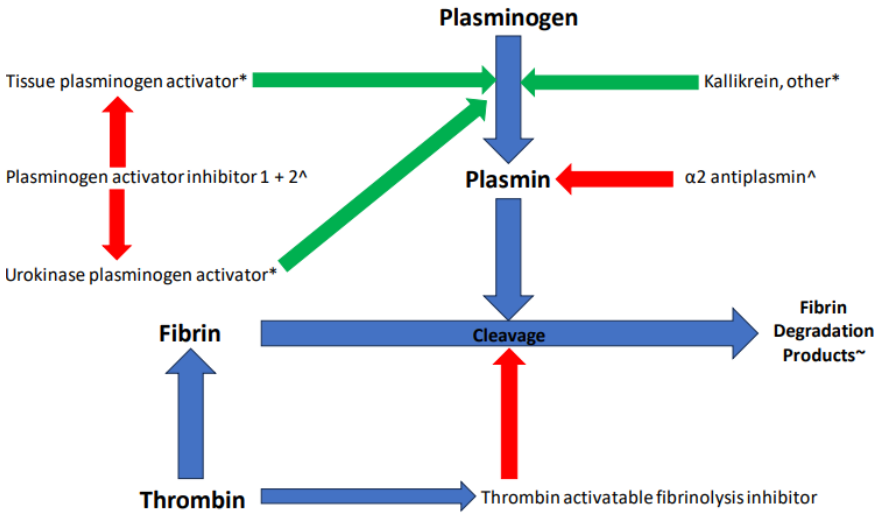

Figure 3 Fibrinolysis pathway and potential mechanisms of AOC. Red arrows show inhibition and green arrows activation. *****Fibrinolysis activation, **^**fibrinolysis dysregulation, **~**dysfibrinogenaemia. PAI-2 is made in the placenta and urokinase is found in amniotic fluid.