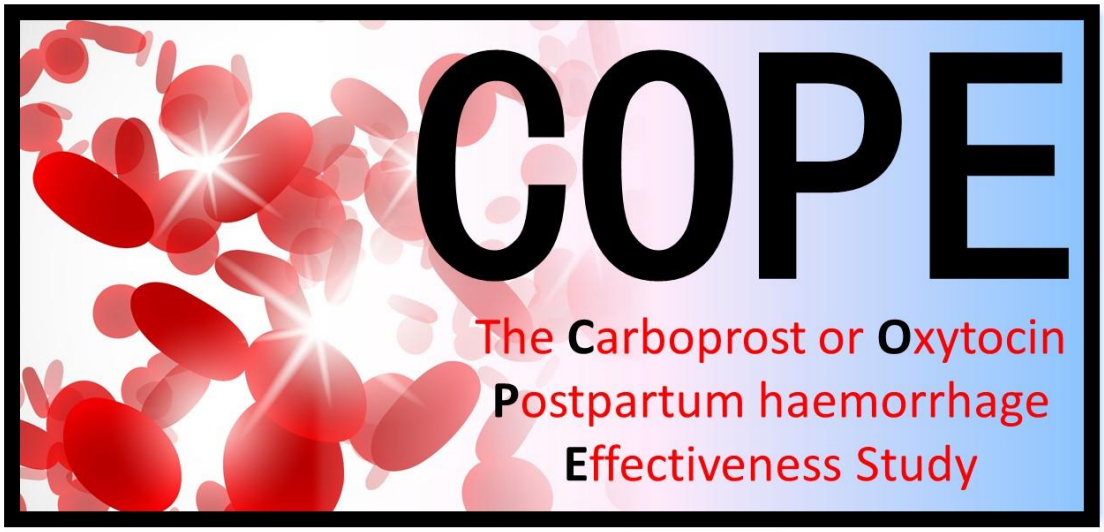

COPE: Carboprost vs Oxytocin as the First Line Treatment of Primary Postpartum Haemorrhage

A Phase IV, double-blind, double-dummy, randomised controlled trial.

COPE Protocol v2.0 10/09/2018

Study Sponsor:

University of Liverpool
Research Support Office
Waterhouse Buildings
3 Brownlow Street
Liverpool L69 3GL
United Kingdom

EudraCT number: 2018-001829-11

CTA Reference Number: Pending

ISRCTN: Pending

Research Ethics Ref:

Sponsor Ref: UoL001337

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** 10/9/18.

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Sanyu Research Unit, Department of Women's and Children's Health
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Authorised on behalf of Sponsor:

Signature: _____ **Date:** 10/09/18

Mr Alex Astor
Head of Research Support
University of Liverpool
Research Support Office
Waterhouse Buildings
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Authorised by Lead Statistician:

Signature: _____ **Date:** 10/09/2018

Prof Carrol Gamble
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General Information
This document describes the COPE trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Clinical Trials Research Centre, University of Liverpool) to confirm they have the most up to date version. Clinical questions relating to this trial should be referred to the relevant Chief Investigator, Professor Andrew Weeks, via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (22) and has regard for the Health Research Authority guidance (1). Regulatory and ethical compliance information is located in section 13.

Relationship Statements
Roles and responsibilities are fully described in section 16.

The sponsor name is University of Liverpool who will formally delegate specific sponsoring roles to the Chief Investigator and Clinical Trials Unit, but remains legally responsible for the trial.

Clinical Trials Unit (CTU): The Clinical Trials Research Centre (CTRC) at the University of Liverpool in collaboration with the chief investigator, Professor Andrew Weeks, will have overall management responsibility for the trial from a CTU perspective and will be responsible for the co-ordination of centres.

Clinical Trials Research Centre as part of the Liverpool Clinical Trials Collaborative has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Clinical Trials Research Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and core standard operating procedures.

Contact Details: Institutions

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Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
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Additional Contacts:

The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File:

Contact	**Document Title**
Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	COPE Trial Oversight Committee Membership
Principal Investigators	COPE Participating Centres

1 TABLE OF CONTENTS

Glossary

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
COS	Core outcome set
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
EUDRACT	European Clinical Trials Database
GP	General Practitioner
HRA	Health Research Authority
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Health Care Products Regulatory Agency
NRES	National Research Ethics Service
NIHR CRN	National Institute for Health Research Clinical Research Network
PI	Principal Investigator
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research & Development
REC	Research Ethics Committee
RM	Research Midwife (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Product Characteristics
SMR	Scottish Morbidity Records
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WHO	World Health Organisation

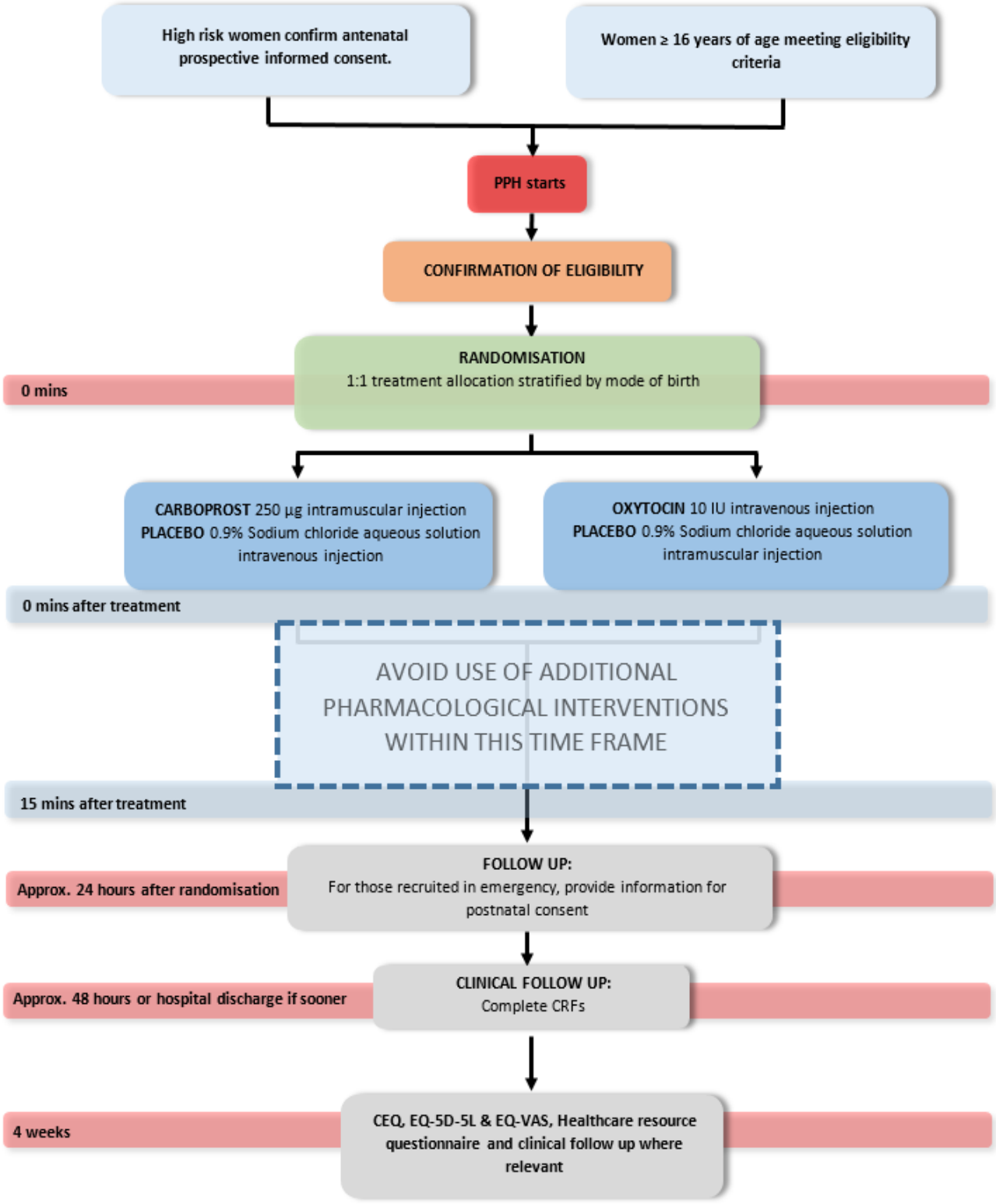
2 PROTOCOL SUMMARY

Full Title:	Carboprost vs oxytocin as the first line treatment of primary postpartum haemorrhage. A Phase IV, double-blind, double-dummy, randomised controlled trial.
Acronym:	COPE
Phase:	IV
Target Condition:	Primary Postpartum haemorrhage (PPH)
Sample size	3,948 participants
Main Inclusion Criteria:	• ≥ 16 years of age • Requirement for medical treatment for primary PPH
Main Exclusion Criteria:	• Known to have opted out of participation antenatally • Known oxytocin or carboprost hypersensitivity • Known active cardiac or pulmonary disease • Known to have previously been treated as part of COPE • Has already received uterotonic drug treatment for postpartum haemorrhage (this does not include PPH prophylaxis) • Stillbirth
Study Centres and Distribution:	NHS hospital maternal units in the UK
Patient Study Duration:	Duration per participant: 4 weeks
Overall Study duration:	48 months
Agent/ Intervention:	**Intervention:** Carboprost 250 micrograms by deep intramuscular injection and 1ml placebo by slow intravenous injection **Control:** Oxytocin 10 international units by slow intravenous injection and 1ml placebo by deep intramuscular injection
Primary objective:	To compare carboprost with oxytocin as initial treatments for women with clinically diagnosed PPH after giving birth in UK hospitals.
Secondary objective:	1. To assess the relative cost-effectiveness of the use of carboprost and oxytocin as initial treatments for women with clinically diagnosed PPH.

	2. To explore the views of participants and their carers about their experiences of the two treatments and the consent process.
Primary outcome measures:	Blood transfusion defined as "Any red blood cell transfusion or cell salvage of ≥300 mls commenced any time between randomisation and 48 hours after randomisation (or hospital discharge if earlier than 48 hrs)"
Secondary outcome measures:	1. Volume of blood transfusion 2. User of a further uterotonic drug 3. Composite outcome of any organ dysfunction based on WHO near-miss approach for maternal health (2) 4. Hysterectomy 5. Blood loss 6. Blood loss ≥ 1000 mls 7. Haemoglobin 8. Shock 9. Maternal death 10. Non pharmacological approach to treat or investigate bleeding 11. Manual removal of placenta 12. Any adverse reactions of the intervention for the mother 13. 'Skin to skin' care with baby within the first hour after birth 14. Separation from new-born in first hour after birth 15. Breastfeeding 16. Childbirth Experience Questionnaire (CEQ) 17. Resource use
Qualitative Study	During the 6-month internal pilot phase and for at least the first 9 months of the main trial we will conduct qualitative research to explore the views and experiences of women recruited to the trial, their partners and practitioners involved in recruitment and consent in COPE.

Protocol Summary – continued

Figure 1: Schematic of Study Design:



3 INTRODUCTION

3.1 Background

Bleeding after childbirth (postpartum haemorrhage, PPH) occurs after around 5% of births (depending on definition) and causes the death of 75,000 women worldwide each year (3). It is the second leading cause of direct maternal deaths in the UK (19 deaths between 2013-2015) (4) and also causes significant maternal and neonatal morbidity.

PPH is a clinical emergency. The bleeding in PPH is unpredictable and difficult to quantify, and so most clinicians treat early, as soon as they are unhappy with the bleeding. As a result of the unpredictability of PPH and difficulties in gaining emergency consent, there are few randomised trials of PPH treatments. The evidence used in guidelines is therefore based largely on studies of prophylaxis and small observational studies (5). The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme has therefore called for research into PPH treatments as one of its research priorities. Recent advances in emergency intrapartum consent pathways, developed in part by applicants in partnership with consumer groups, have facilitated recruitment (6-9).

3.2 Rationale

PPH is a common and potentially serious problem affecting 1 in 20 women. Each year it causes the death of 75,000 women worldwide. It is the second leading cause of direct maternal deaths in the UK (19 deaths between 2013-2015) (4). Significant maternal morbidity may also result from weakness secondary to anaemia, delayed recovery, psychological trauma, difficulties with breastfeeding and poor bonding with the newborn. Available treatments, including drugs with known side effect profiles, blood transfusion and invasive or surgical procedures such as hysterectomy can have substantial negative impact on the woman's recovery, long-term health and sense of wellbeing.

As uterine atony is the most common cause, intravenous (i.v.) oxytocin is universally recommended as first line therapy. However, the recommended dosage varies. Whilst the National Institute for Health and Care Excellence (NICE) recommends 10 international units i.v.; the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines and *Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK* (MBRRACE-UK) suggest 5 international units (5, 10, 11). There are no direct comparisons of the two doses. Although studies suggest that 3 international units is adequate (12, 13), we will use the higher dose in this study to prevent criticism of inadequate dosing. The only risk of this is hypotension that occurs with rapid injection and the need for slow intravenous injection will be emphasised in training (see 3.2.1 below).

The PPH rate is increasing, and this may be partially related to the overuse of oxytocics in labour (11). Laboratory studies on myometrium suggests that repeated use of oxytocics leads to the saturation of oxytocin receptors and reduced efficacy of oxytocin as a therapy (14). Attention has therefore turned to the use of prostaglandins as an alternative mechanism for improving the strength of uterine contractions in the event of uterine atony. Misoprostol is a prostaglandin E1 analogue, which is convenient for both storage and administration. It has been studied extensively for both prophylaxis and treatment of PPH, and found to be less effective than oxytocin (3) and of no additional benefit when given in addition to standard drugs for PPH treatment (15). Carboprost is a prostaglandin F2a analogue that is given intramuscularly (i.m.). There are 13 small studies of carboprost for

PPH prophylaxis. They show a reduction in blood loss compared with conventional uterotonics, but diarrhoea, vomiting, fever or hypertension affects about 15% of those treated (16). Carboprost is also more expensive than oxytocin. There are no studies of carboprost for PPH treatment (17), but NICE recommends carboprost as a second line treatment. NICE, and others, have suggested the need for a major randomised trial to ascertain both the effectiveness of carboprost and its optimal position in a PPH treatment pathway (3, 5).

3.2.1 Risk and Benefits

Oxytocin is the standard first line treatment for atonic postpartum haemorrhage. It has been shown to cause effective uterine contraction, is low cost and relatively free from side-effects. Oxytocin can commonly cause headache, nausea and vomiting. The benefit of repeated doses (for example giving 10iu prophylaxis and then 10iu treatment shortly after) has however been questioned (3, 14), especially given that pharmacokinetic studies suggest that the optimal dosage is just 3iu (12). Furthermore, a bolus dose of intravenous oxytocin causes a rapid but transient fall in blood pressure by around 20mmHg (18) and has been implicated in maternal death during PPH (CEMD 2001). Repeated doses of oxytocin also cause water retention. It is therefore of uncertain benefit, and not without risks.

Carboprost, a prostaglandin F2α analogue, is usually reserved for second line management of atonic PPH. A systematic review of 13 small randomised trials comparing the efficacy of carboprost and conventional uterotonics for PPH prophylaxis found that it was associated with less blood loss, but around 15% of women suffered side effects including diarrhoea, vomiting, fever or hypertension (16).

3.3 Objectives

3.3.1 Primary Objective

The aim of the research is to compare intramuscular carboprost 250 micrograms with intravenous oxytocin 10 international units for the initial treatment for women with clinically diagnosed postpartum haemorrhage after giving birth in UK hospitals.

3.3.2 Secondary Objective(s)

1. To assess the relative cost-effectiveness of the use of carboprost and oxytocin as initial treatments for women with clinically diagnosed PPH.
2. To explore the views of participants and their carers about their experiences of the two treatments and the consent process.

3.4 Outcome measures

The outcomes selected for this study include the recently developed Core Outcome Set (COS) for PPH treatment trials (Appendix 1).

Primary Outcome

Blood transfusion defined as 'any red blood cell transfusion or cell salvage of ≥ 300mls commenced any time between randomisation and 48 hours after randomisation (or hospital discharge if earlier than 48 hours'.

3.4.1 Secondary Outcome

All secondary outcomes collected prior to discharge or 4 weeks whichever is earliest unless otherwise specified.

1. Volume of blood transfusion

2. Use of a further uterotonic drug

3. Composite outcome of any organ dysfunction[1]

4. Hysterectomy

5. Blood loss ≥ 1000 mls

6. Haemoglobin

7. Shock

8. Maternal death

9. Non-pharmacological approach to treat or investigate bleeding[2]

10. Manual removal of placenta

11. Any adverse reactions of the intervention for the mother

12. Skin to skin care with baby within the first hour after birth

13. Separation from new-born in first hour after birth

14. Breastfeeding

15. Childbirth Experience Questionnaire (CEQ)

16. Resource use[3]

During the internal pilot phase and for at least the first 9 months of the main trial we will conduct qualitative research to explore the views and experiences of women recruited to the trial, their partners and practitioners involved in recruitment and consent in COPE.

[1] Based on definitions within the WHO Maternal 'near-miss' Approach for maternal health (2).

[2] Interventions include: laparotomy, internal uterine tamponade using a Bakri balloon or uterine packing, arterial embolization to treat excessive bleeding, and examination under anaesthetic for excessive bleeding.

[3] Number of units of blood transfused will be collected for resource use; transfers to higher care units will be collected within resource use.

4 TRIAL DESIGN

This is a double-blind, double-dummy, randomised controlled trial.

To determine the feasibility of answering the clinical question, an internal pilot in 5 UK hospitals, examining rates of recruitment and consent, data completeness and sample size assumptions will be carried out.

Criteria for progression from internal pilot to full study are:

Recruitment
Taking into account the pilot study and the ratio of vaginal to caesarean births, we will estimate the total recruitment period required to achieve the target sample size. If this is 30 months or less, then we will proceed to the main trial. If 30 to 42 months, we will introduce ways to reduce this, then proceed to main trial. If over 42 months and with no obvious solutions, then we will abandon the main trial.

Consent
If the rate of informed consent for follow-up and data use is 80% or more, proceed to main trial. If 60% to 80%, then review qualitative data to identify any aspects amenable to change, and proceed. If less than 60%, and no obvious solutions exist, then abandon the main trial.

Completeness of primary outcome data
If primary outcome data are available for over 95% of participants, then proceed. If 75-95%, identify aspects amenable to change and proceed to main trial as amended. If available for less than 75% of participants randomised, and no obvious solutions exist, abandon the main trial.

Sample Size estimation
The Independent Data Safety and Monitoring Committee (IDSMC) will be asked to review the assumptions made in the sample size calculation. As a result the numbers required may be increased but not decreased. If an increase in sample size is recommended, then this will be discussed with funders and informed by ability to deliver within time and budget.

5 STUDY SETTING AND SELECTION OF CENTRES / CLINICIANS

The study will take place in up to 40 UK hospital maternity units.

5.1 Selection of Centres/Clinicians

Criteria for the selection of centres will be determined by the Trial Management Group (TMG) and will be described in the supplementary document 'COPE Site Suitability Assessment'.

Initiation of centres will be undertaken in compliance with Clinical Trials Research Centre (CTRC) Standard Operating Procedures (SOPs). Centres fulfilling the criteria will be selected to be recruitment centres for the COPE trial and will be opened to recruitment upon successful completion of all global (e.g. Research Ethics Committee (REC) and Medicines and Healthcare Products Regulatory Agency (MHRA)) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTRC as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in a log, maintained separately to the protocol.

6 STUDY POPULATION

The requirements of Good Clinical Practice (GCP) are that a doctor should either recruit or supervise the recruitment of individuals to a Clinical Trial of an Investigational Medicinal Product (CTIMP). Thus women giving birth at home or in stand-alone midwifery units will not be eligible to participate.

6.1 Inclusion Criteria

- ≥ 16 years of age
- Requirement for medical treatment for primary PPH

6.2 Exclusion Criteria

- Known to have opted out of participation antenatally
- Known oxytocin or carboprost hypersensitivity
- Known active cardiac or pulmonary disease
- Known to have previously been treated as part of COPE
- Has already received uterotonic drug treatment for postpartum haemorrhage (this does not include PPH prophylaxis)
- Stillbirth

6.3 Co-enrolment Guidelines

Individuals who are currently recruited into other intrapartum interventional studies may be approached for the COPE trial upon agreement with the study Chief Investigator. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the COPE trial this must first be discussed with the CTRC who will contact the Chief Investigator, Prof Andrew Weeks.

7 SCREENING, RECRUITMENT AND RANDOMISATION

7.1 Screening

Anonymised screening information on patients who are assessed for eligibility (whether or not they consent or are randomised) will be collected by completion of a participant screening form. These screening forms will provide important information for monitoring purposes and possible reasons for non-randomisation.

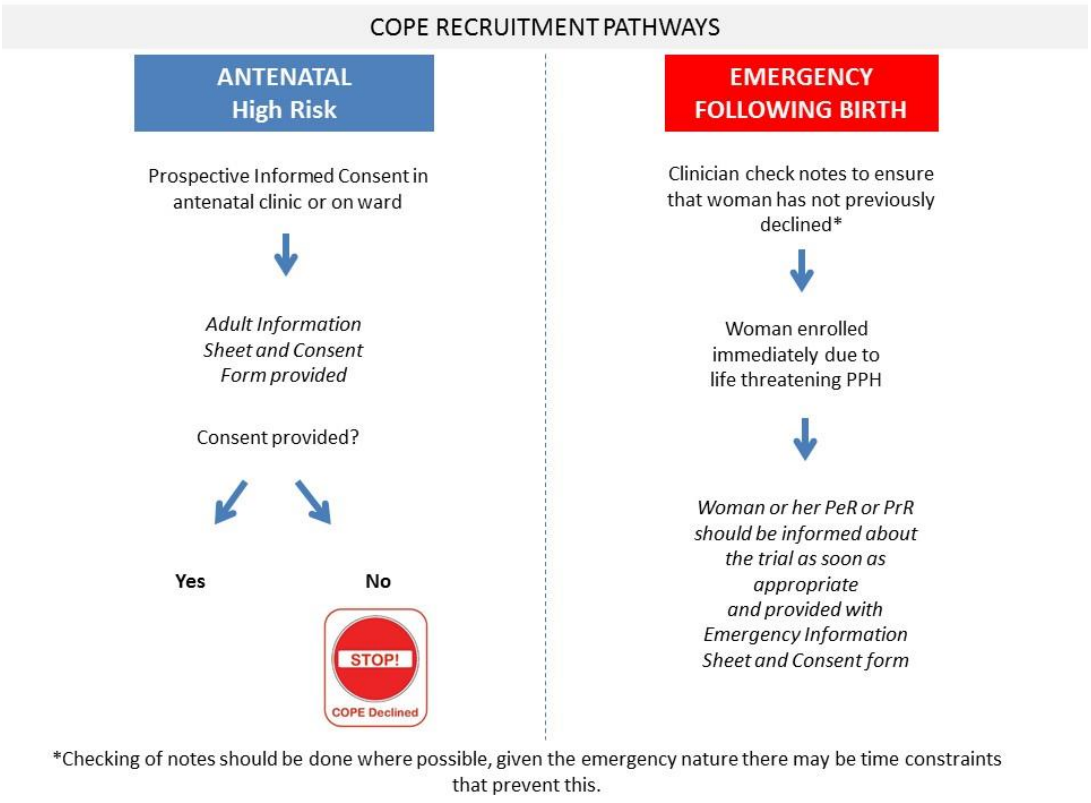
7.2 Recruitment Pathways

PPH is an unpredictable clinical emergency occurring after around 5% of births. Whilst it is possible to identify those women who are at higher risk of PPH it is not logistically feasible to approach all women antenatally and obtain prior written informed consent. COPE therefore has adopted a pragmatic approach in order to ensure that women at greatest risk of PPH (and therefore most likely to be eligible to be randomised) have the opportunity to consider trial entry in the antenatal period. It will be at the treating clinician discretion to identify women at high risk of PPH.

COPE participants will be recruited via two pathways:

Figure 2: COPE recruitment pathways

(PeR = Personal legal representative; PrR = Professional legal representative – see text for definitions)



7.2.1 Antenatal Information for Women at high risk of PPH

Where women are identified as being high risk informed consent will be sought ideally at the antenatal stage. For the purposes of this study, 'increased risk of bleeding' will refer to those antenatal risk factors with a odds ratio of >3, i.e. placenta praevia, multiple pregnancy, pre-eclampsia or previous PPH (19). For women in whom informed consent is not sought antenatally they may be randomised when they meet the inclusion criteria after child birth and consent sought afterwards for use of the data and continued follow-up.

7.2.2 Antenatal Information Provision for other women

A variety of strategies will be used to advertise the study to raise awareness amongst women, including: leaflets in case notes, antenatal clinics, social media campaigns, posters, newsletters and emails.

Study advertising will include details of how women can contact the local study team to discuss the study.

7.3 Consent Procedures

Consent procedures for COPE are tailored to be appropriate for the applicable recruitment pathway. In both pathways information will be provided in the antenatal period, however informed consent is initiated prior to labour only in women identified to be at high risk of PPH:

1. Women identified to be at high risk of PPH (see definition in 7.2.1 above): written informed consent for randomisation, treatment and follow-up will be obtained in the antenatal period.
2. Other women: Randomisation and treatment will occur if eligibility criteria are met after child birth and written informed consent for the use of relevant data and for follow-up will be obtained in the postnatal period.

The consent procedure in COPE study is summarised in Figure 2. Information on different COPE study consent types is provided to sites separately from the protocol.

7.3.1 Principles of informed consent

In obtaining and documenting informed consent, the investigator/delegate should comply with applicable regulatory requirements and should adhere to the principles of GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

At the appropriate time, the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients or their legal representative by staff with experience in obtaining informed consent. Patient Information Sheet and Consent form, describing in detail the trial interventions, trial procedures and risks will be approved by a REC and the patient (or patient's Legal Representative) will be asked to read and review the document. Upon reviewing the document, the investigator will explain

the research study to the patient (or patient's Legal Representative). This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All patients (or their Legal Representative) will be given opportunity to ask any questions that may arise, and should have the opportunity to discuss the study with their friends and family, and time to consider the information prior to agreeing to consent. A contact point where further information about the trial may be obtained will be provided.

Patients will have as long as they need to consider participation in COPE (in the high risk group this should happen ideally prior to labour). In the postnatal pathway research staff should aim to meet the woman to seek consent within 24 hours, or prior to discharge or transfer to another hospital. The patient or patient's Legal Representative will be asked to sign and date the informed consent document. Both the person obtaining consent and the patient (or patient's Legal Representative) must personally sign and date the form. A copy of the consent form will be given to the patient (or patient's Legal Representative) for their records. The original copy will be filed in the Investigator Site File, a copy filed in the patient's notes and a further copy should be sent to the CTRC.

The participant (or participant's Legal Representative) may, without being subject to any resulting detriment, withdraw consent for trial participation any time by revoking their informed consent. In this circumstance or where the patient (or patient's Legal Representative) declines to provide consent the rights and welfare of the patient will be protected and the quality of medical care will not be adversely affected. If consent is declined, or withdrawal occurs in the antenatal period then a small sticker will be placed on their handheld notes as per section 7.3.2.

7.3.2 Antenatal Consent for Women at high risk of PPH

As shown in Figure 2, women identified to be at high risk of PPH attending antenatal clinics will be approached about the study and provided with an information sheet and consent form. For the purposes of this study, 'increased risk of bleeding' will refer to those antenatal risk factors with an odds ratio of >3 (see section 7.2.1). There will be an opportunity to have any questions about the study answered by an appropriate health care professional on the COPE delegation log. This will be either directly, or after the recruitment discussion by 'phone-back' service, email, telephone or social media.

If a woman has made a decision prior to labour not to participate, then a sticker (see Figure 3) will be placed on their handheld notes to communicate this decision to decline participation to the clinical team. A sticker will also be used where consent is provided but then subsequently withdrawn prior to labour.

If the emergency situation allows, women who have provided written informed consent during pregnancy will be reminded of this when they meet the inclusion criteria after child birth. A verbal indication of objection to continuing in the study will be respected and usual care will continue.

Figure 3: Sticker for hand-held case notes.

7.3.3 Postnatal consent for other women

Once a woman has been diagnosed with PPH, a critical clinical emergency situation exists. Eligible women have a life threatening condition and risk of death is highest early after delivery. Their mental capacity, physical and emotional state may be diminished as a result of blood loss, pain, or by drugs administered during the labour.

Women will be randomised into the trial in the emergency situation where treatment needs to be given urgently and there is no time for prior consent from a Legal Representative. An overview of the emergency recruitment and consent procedure following birth is provided in Figure 2. The treating clinician may briefly explain the study to the woman if it is deemed appropriate. Note that it is not the intention to obtain verbal consent in this emergency situation.

7.3.3.1 Consent provision where capacity is regained promptly

Postnatally, once the woman is stable and ideally within 24 hours or prior to discharge / transfer to another hospital, full study information will be provided to the woman. Before approaching women, the trial recruiter will firstly check whether the timing is appropriate with the clinical team. Permission will be sought for participation in study follow-up. The participant will be asked to sign the emergency consent form.

7.3.3.2 Consent provision where capacity is not regained or is delayed

Before approaching women, the trial recruiter will firstly check whether the timing is appropriate with the clinical team. Should it be apparent that incapacity is likely to continue, full study information will be provided as soon as practicable to her Personal Legal Representative (PeR) or Professional Legal Representative (PrR), if PeR is not available. The PeR or PrR will be asked to sign the applicable emergency representative consent form.

The consent given by an appropriate legal representative on behalf of an adult lacking capacity to do so for themselves shall represent the presumed will of the incapacitated adult and as such it is not mandatory to re-approach adults recruited in such a manner should they regain their capacity to give consent during the course of their participation in COPE.

Legal representatives will be made aware that, should this circumstance arise during the trial participation period (4 weeks), the adult will be provided with information about COPE but will not be approached to provide their own written consent. The adult participant will be made aware that they can withdraw from the trial at any time by revoking the informed consent provided by their legal representative.

7.3.3.3 Definitions of legal representatives

England and Wales:

- Personal Legal Representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. If one is not available:
- Professional Legal Representative i.e. a person not connected with the conduct of the trial who is the doctor primarily responsible for the medical treatment of the adult, or a person nominated by the healthcare provider.

Scotland:

- Personal Legal Representative i.e.
    - Adult's Welfare Guardian or Welfare Attorney, or if not appointed:
    - The adult's nearest relative, if neither are reasonably contactable:
- Professional Legal Representative i.e. a person not connected with the conduct of the trial who is the doctor primarily responsible for the medical treatment of the adult, or a person nominated by the healthcare provider.

7.3.4 Discharge / transfer to another hospital prior to emergency consent

It is expected that consent will be sought for all participants prior to discharge/transfer to another hospital (if the participant dies prior to consent being sought refer to section 7.3.5).

In the rare instances where consent is not sought prior to discharge/transfer the following should occur:

The Research Midwife (RM), or other designated member of the research team at site, will call the participants within 5 working days of randomisation to inform the participant of their involvement in the trial and provide details of the trial.

Note: Audio-recordings of telephone discussions are not required.

Once the telephone call has been completed, the RM, or other designated member of the research team at site, will post within 5 working days as applicable:

- Participant covering letter to home
- Participant information sheet and consent form (Home)

The covering letter will confirm that the participant has 4 weeks from the date of the letter to return the consent form confirming whether they would like to continue participation in the trial.

If no response is received within 2 weeks (14 days), the RM, or other designated member of the research team at site will make a follow up call to the participant to check that they have

received the information and request that the consent form be returned within 5 working days if they would like to continue participation in the trial. Written information and a consent form will be re-sent if the site team member is unable to contact the participant or information has not been received.

If no response is received within 4 weeks (28 days), the participant's data will not be included within the trial as confirmed in the telephone conversation/covering letter. Consent is being sought in this scenario for the disclosure of confidential information in order to avoid a breach of the common law duty of confidentiality. If we find that consent in this scenario is not practicable and results in informative missing data (e.g. linked to severity of condition or duration of hospital stay) a future Section 251 application may be made.

7.3.5 Maternal death prior to emergency consent

This is likely to be a very rare occurrence. However, when a participant dies before consent has been sought, the attending RM will obtain information from colleagues and bereavement counsellors to establish the most appropriate practitioner to notify the Personal Legal Representative of the research involvement.

Consent can be sought from Personal legal representatives following the death of their relative and prior to the Personal Legal Representative's departure from the hospital. However, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Personal Legal Representative Information Sheet and Consent Form would be used.

If consent is not sought prior to the Personal Legal Representative's departure from hospital then the Personal Legal Representative will be notified and consent can be sought by an appropriate practitioner at bereavement follow-up visit.

In addition, all deaths, irrespective of the consent status, should be reported on a Serious Adverse Event Case Report Form (CRF) and faxed to the CTRC within 24 hours of the research team becoming aware (see section 11.3.4).

7.3.6 Neonatal death prior to emergency consent

This is likely to be a rare occurrence. However, if a participant experiences the death of their baby before consent has been sought, the attending RM will obtain information from colleagues and bereavement counsellors to establish the most appropriate practitioner to notify the participant of the research involvement.

Consent will be sought if considered appropriate; however, it is at the discretion of the site staff to determine if this is appropriate for each individual participant. In this situation, the usual information sheet and consent form would be used.

7.4 Randomisation Procedures

Participants will be randomised in a 1:1 ratio using random variable block size, stratified by mode of birth (caesarean section or vaginal birth).

Centres will be provided with a series of sequentially numbered, sealed treatment kits to be received by the pharmacy department and distributed to an appropriate secure location within delivery suite for ready access upon presentation of eligible patients.

Each kit will contain either:

a) A vial of carboprost and a vial of placebo or
b) A vial of oxytocin and a vial of placebo.

Departments will be provided with CRFs to be completed promptly at the time of recruitment (to document key screening/eligibility and baseline data). The blank CRFs should be stored alongside the treatment kits.

After eligibility is confirmed by an authorised medical doctor, the next sequentially numbered treatment kit should be selected and administered. The treatment kit's identification number is the randomisation number for the participant and should be recorded in patient's medical notes and on the trial CRFs.

Pharmacy will periodically check to ensure that there are adequate stocks of trial treatment kits, that the correct number of treatment kits are present and intact and that the sequential numbering system is maintained. Any discrepancies will be immediately reported to the CTRC.

7.5 Who is Blinded to Allocations

This is a double-blind study and all individuals involved in the conduct and delivery of the trial, except for the randomising statistician, or those unblinded to individual cases as a requirement (e.g. for safety reporting), will be blinded to treatment allocations. Statisticians involved in monitoring will be unblinded following determination of participant inclusion within each analysis population.

In case of the need of emergency unblinding, unblinding envelopes will be provided and stored at an agreed location within the site that is readily accessible at time of need. The construction of these envelopes is resistant to accidental damage or tampering and contents cannot be viewed without fully opening.

Pharmacy will periodically check to ensure that the appropriate number of unblinding envelopes are present and intact. Any discrepancies will be immediately reported to the CTRC.

For unblinding procedures see section 10.8.

8 PARTICIPANT TIME LINE, ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up

Participants will be recruited and followed up to a maximum of 6 weeks postnatally.

		Follow-Up Schedule				
Procedures		**Screening**[1]	**Baseline (T0)**[2]	**T0 + 24 hrs**	**T0 + 48 hrs or hospital discharge if sooner**	**T0 + 4 wks**[6]
Assessment of Eligibility Criteria		X	X			
Signed Consent Form[1]		X				
Confirmation of Full Eligibility by an authorised medical doctor			X			
Randomisation			X			
Administration of Study Intervention			X			
Signed Consent Form[3]				X		
Clinical outcomes	Blood transfusion or cell salvage				X	
	Volume of blood transfusion				X	
	The use and timing of additional uterotonics			X	X	
	Outcome of any organ dysfunction				X	(X)
	Blood loss at birth			X	X	
	Shock			X	X	
	Hysterectomy				X	(X)
	Maternal death		(X)	(X)	(X)	(X)
	Non-pharmacological approach				X	
	Manual removal of placenta				X	
	Skin to skin care with baby			X		
	Separation from new-born in first hour after birth			X		
	Breastfeeding			X	X	X
Clinical Laboratory	Haemoglobin[5]			X	(X)	
	Coagulopathy				(X)	
Assessment of Adverse Reactions[7]				X	(X)	(X)
Childbirth Experience Questionnaire						X
EQ-5D-5L questionnaire and EQ-VAS				X		X
Healthcare resource utilisation						X

(X) – As indicated/appropriate.

[1] Only for women at high risk of PPH

[2] At baseline, all procedures should be done before study intervention.

[3] Emergency consent is obtained after childbirth ideally within 24 hrs or prior to discharge / transfer to another hospital. If consent is not obtained prior to discharge, the appropriate consent procedures should be followed as per section 7.3.
[4] It is only the assessment of blood transfusion or cell salvage that is done at 48 hrs. All other assessments are done after hospital discharge, unless indicated otherwise.
[5] Haemoglobin (in non-transfused women only) will be ideally obtained postnatally on the day following birth (12-36 hours post birth) or at discharge, whichever is soonest. For more details, see section 8.2.
[6] Participant to be contacted initially using her favoured mode of communication (letter, email or telephone), with a letter or telephone reminder if no response within 2 weeks
[7] Adverse reactions as per Appendix 1 will be collected at 24 hrs. SARs will be reported throughout the study.

8.2 Procedures for Assessing Efficacy

Clinical efficacy outcomes will be collected at 24 hours and at 48 hours or at hospital discharge, if sooner. Details of the outcomes (with the timing of assessment and definitions) are included in Appendix 1. COPE OUTCOMES.

8.3 Procedures for Assessing Safety

The Principal Investigator (PI) or delegated research staff will be monitoring and reporting all relevant adverse events (see section 11) from randomisation until 48 hours or at hospital discharge, if earlier. Adverse events will also be monitored at follow-up.

8.4 Other Assessments

8.4.1 Childbirth Experience Questionnaire (CEQ)

The CEQ was developed in 2010 to measure the impact of an intervention on a woman's childbirth experience. It includes four main aspects of the childbirth experience: Own capacity, Professional support, Perceived safety and Participation.

In COPE study the UK-validated CEQ will be completed by the participants as a paper questionnaire at 4 weeks.

8.4.2 Health Economics assessments

8.4.2.1 Resource use and costs

Resource use will be based on:

(1) Entries made in designated sections of participants' CRFs. The CRF will be used to record data on procedures (surgical) and interventions (including units of blood products transfused) as well as dates of patient admission and discharge. This will be completed by the RM at discharge.

(2) A cost questionnaire, administered at the 4-week follow-up, using the participant's favoured mode of communication (letter, telephone, email), with a letter or telephone reminder if no response provided within 2 weeks.

(3) Hospital Episode Statistics (HES) and Scottish Morbidity Records (SMR) data sourced from i) NHS Digital for participants recruited in England; ii) NHS Wales Informatics Service for participants recruited in Wales; and iii) the electronic Data Research and Innovation Service for participants recruited in Scotland.

- Participants will be fully and unambiguously informed as to the transfer of any personal data associated with obtaining and processing HES and SMR data.
- The following data will be collected from the above listed NHS organisations: outpatient, inpatient (including critical care) and A&E attendances by each participant from 3 months prior to randomisation, to 4 weeks post randomisation (following completion of follow-up). Participant information (postcode, date of birth, NHS (or CHI) number, trial number and sex) will be collected by CTRC within a secure database which will enable CTRC to request HES and SMR data from NHS Organisations. The database will only be accessible by authorised personnel working on the trial or shared with authorised personnel working at the NHS organisations. At the time of the data request, the database will be sent to authorised personnel at the NHS organisations via a secure link and the HES and SMR data with the trial number will be securely transferred to health economists at Centre for Health Economics and Medicines Evaluation (CHEME), Bangor University, who will be conducting the economic analysis. The NHS organisations will be asked to remove participant personal identifiers such as NHS number, date of birth, pseudoHESID at source.

The only identifier present in the dataset will be the trial randomisation identifier and health economists at CHEME will not have any access to keys linking this to participant personal data. Access will be restricted only to health economists working on the trial, and data will only be accessed by username and password. Once the analysis has been completed the HES and SMR data will be securely disposed in accordance with the CHEME and NHS organisations Data Services for Commissioners (DSfC).

Unit costs will be obtained from NHS reference costs and other standard NHS sources.

8.4.2.2 Health outcomes

Quality Adjusted Life Years (QALYs) will be estimated from utilities derived from trial participant responses to EQ-5D-5L questionnaires (and applying recommended methods for generating UK relevant utilities) administered by the RM at 24 hours and completed by the trial participant at 4-weeks follow-up.

8.5 Patient Transfer and Withdrawal

8.5.1 Discontinuation

Upon completion of trial intervention, treating physicians are asked to avoid additional pharmacological treatment for 15 minutes (please refer to section 10.3.2). If a participant continues to experience bleeding despite the completion of the trial intervention after this time, they should be treated with additional therapies as per the local protocol for the treatment of this condition. Those treatments relevant to the outcomes of this trial will be recorded. This would **not** necessitate the participant discontinuing the study.

8.5.2 Withdrawal of Consent

Generally, follow-up will continue unless the participant / Legal Representative explicitly withdraws consent for follow-up (see section 7.3).

The participant / Legal Representative is free to withdraw consent at any time without providing a reason and without being subject to any resulting detriment. The rights and welfare of the participant will be protected by emphasising to them throughout the trial that the quality of medical care will not be adversely affected if they decline to participate in the trial, or withdraw consent.

Where the participant / Legal Representative wishes to withdraw consent, a withdrawal CRF should be completed documenting the reason for withdrawal. Centres should explain the importance of remaining in trial follow-up and of the importance of contributing data.

8.5.3 Participant Transfers

A minority of participants may be randomised and treated at a COPE site and then transferred to another hospital for further treatment before the 48-hour follow-up period is completed (e.g. the participant needs to be transferred to a hospital with intensive care facilities).

In these cases, the treating hospital should contact the transfer hospital to collect the follow-up information and consent (where possible).

Note: Only transfer sites that are also a recruiting site for COPE can assist with the consent process, however, regardless of where consent was sought, the participant would be classified as a recruited participant for the treating site only.

8.6 Loss to Follow-up

Follow-up contact will be made via the PI or designated research staff at each centre. After discharge, participants will be contacted via their preferred means of communication for the purposes of the 4-week follow-up.

Non-responders will be contacted again after 2 weeks. Failure to respond to the second contact within another 2 weeks will deem the participant “loss to follow-up”.

Wherever possible, information on the reason for loss to follow-up will be recorded

8.7 Trial Closure

The end of the trial is defined to be the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

9 EMBEDDED MIXED METHODS RESEARCH

9.1 Design

During the internal pilot phase and for at least the first 9 months of the main trial we will conduct interviews, focus groups, audio-recorded recruitment discussions and questionnaires to explore the views and experiences of women recruited to the trial, their birth partners and practitioners involved in recruitment and consent in COPE. This research will explore:

- experience and acceptability of the trial and its interventions;
- antenatal information provision;
- practitioner experience of recruitment;
- the interaction and exchange of information about the trial between staff and potential participants;
- emergency consent at time of PPH;
- antenatal consent amongst both those recruited and not recruited;
- postnatal consent for the use of data and follow-up.

Interim findings from research conducted in the internal pilot will be used to inform approaches to recruitment and consent procedures for the main trial.

Methods will include:

A: Audio recording of COPE antenatal consent discussions between women and their birth partner (if applicable) and trial recruiters.

B: Interviews with women and their birth partners (if applicable) who agree or decline consent including bereaved parents

C. A questionnaire with women and their birth partners (if applicable) who agree or decline consent.
D: Focus groups and/or interviews with COPE trial recruiters at each pilot site.

9.2 Selection of participants

Woman and birth partners

Inclusion criteria

- Women and their birth partners who are recruited to COPE

Exclusion criteria

- Women and their birth partners who do not speak English or lack the capacity to consent

COPE practitioners

Inclusion criteria

- Practitioners who are involved in screening, recruiting, randomising and consenting participants/ legal representatives

Exclusion criteria

- None

Table 9.2 Qualitative Study Applicability

Consent sought from	Location consent was sought	A: Audio-recording	B: Questionnaire	C: Interview
Woman and their birth partner (if present) who do and do not give consent for the main trial	On-site (antenatal and postnatal following birth)	✓	✓	✓
Bereaved women and their birth partner (if applicable)	On-site (postnatal)			✓
Woman and their birth partner (if present)	Home (postnatal)		✓	✓
Bereaved women and their birth partner (if applicable)	Home (postnatal)		✓	✓

9.3 Enrolment and procedure

9.3.1 Part A: Audio-recordings

Delegated COPE recruiters will seek verbal permission to audio-record recruitment consultations when they first approach potential participants and their birth partners about COPE in antenatal and postnatal settings. If permission for audio-recording is declined the recruitment consultation will not be recorded. If permission is given, the recruiter will activate an audio-recorder. If there is more than one trial discussion (e.g. an initial discussion followed by a full trial discussion after women has considered the trial information) then all discussions should be recorded.

Completed audio-recordings will be uploaded to the 'Voicescript' website (http://www.voicescript.co.uk/file-manager/) for transcription. The 'Guidance for the management of audio recordings' should be used to ensure that the recordings are correctly stored and uploaded in accordance with the Data Protection Act.

Audio-recording of trial consultations will take place at each pilot site until the sample target (data saturation point) is achieved. Sites will be informed when audio-recordings can stop.
Note: Please refer to table 9.2 for audio recordings applicability.

9.3.2 Part B: Questionnaires

At antenatal and postnatal recruitment discussions COPE recruiters will ask all women and their birth partners (including those who decline consent) to complete the COPE recruitment questionnaire, place it in a sealed stamped addressed envelope and return it to the recruiter to post to qualitative researcher.

If consent has been given to complete a questionnaire within the COPE information sheet and consent form, but a questionnaire has not been received, the questionnaire will be sent via post or email at the point at which an interview is arranged (if applicable). In the rare instance that main trial consent is not sought prior to discharge/transferred to another hospital, the questionnaire should be sent to women and their birth partners along with the COPE information sheet and consent form to complete.

Recruitment for questionnaires will be conducted for the internal pilot and for at least the first 9 months of the main trial. We anticipate to collect approximately 500 questionnaires.

Note: Refer to table 9.2 for questionnaire applicability.

9.3.3 Part C: Interviews with women and their birth partner

COPE recruiters will ask women and their birth partners to provide contact details on the COPE consent form if they wish to take part in a telephone interview or face-to-face interview (if they live in the Northwest of England). We aim to interview a selection of women and their birth partners recruited through the antenatal and emergency consent procedures who decline consent, provide consent and receive the study intervention.

The researcher will make contact with women and, if possible, their birth partner (if applicable) after the birth to arrange telephone interviews or face-to-face interviews (Northwest only) at their home or location of choice (e.g. hospital, University) approximately 2 to 4 weeks after they have given birth. Birth partner consent will be verbally sought and recorded prior to interview. Telephone interviews with women and their birth partners will be conducted separately. Those involved in face-to-face interviews can choose to be interviewed together. Bereaved women will be contacted no less than six weeks after birth. Such calls will be handled with sensitivity and interviews will be arranged within a timeframe tailored to individual women.

All interviews will be conducted by qualitative researchers who have proven skills in the conduct of research in sensitive settings. Any distress during the interviews will be managed with care and compassion and participants will be free to decline to answer any questions that they do not wish to answer or to stop the interviews at any point. Any such women will be supported in obtaining appropriate help.

Interviews will be conducted in the internal pilot phase (approximately 10-15) and the first 9 months (approximately 15-25 depending upon point of sample (pilot only) or data saturation, whereby no new themes are emerging in the analysis of data). It is expected that the interviews will take on average between 30 to 60 minutes.

After the interviews are complete, participants will be sent a thank you letter and a £30 high street shopping voucher to thank them for their time. All women who express an interest in taking part but are not selected for an interview will be contacted via email (if address provided) to thank them for their interest in the study.

9.3.4 Part D: Focus groups and/or interviews with the COPE practitioners

COPE practitioners (e.g. recruiters, PI or lead RM) at the five pilot sites will be sent an email invitation to participate in a focus group or telephone interview (whichever is possible to arrange around clinical practice).

Those who register interest will be sent a practitioner information sheet including details of topics that will be discussed in the focus group or telephone interview including:

- acceptability of the trial;
- experience of recruitment and the approach to consent;
- potential barriers to recruitment and any potential solutions;
- how information about the trial is communicated to women;
- how women respond to trial information and any suggested improvements to trial information and consent processes.

All interviews will be conducted by the qualitative researcher:

Consent will be sought from participants before the focus group or telephone interview begins. This will involve the qualitative researcher explaining the aims of the study to the practitioner and providing an opportunity for questions. For focus groups, consent forms will be collected from practitioners and checked by qualitative researcher before the focus groups begin. For telephone interviews, the qualitative researcher will read each aspect of the consent form, including consent for audio recording of the interview and ask whether the participant would like to receive a copy of the findings when the study is complete. The

qualitative researcher will tick each box on the consent form when the participant provides verbal consent. Informed consent discussions will be audio recorded for analysis.

Participation will be entirely voluntary and practitioners will be able to withdraw at any time without giving a reason.

After the interviews are complete, site research staff will be sent a thank you letter.

10 TRIAL TREATMENTS

10.1 Introduction

This is a randomised, double-blind, double-dummy trial. The investigational medicinal products (IMPs) in this trial are carboprost and oxytocin. Participants will be randomised to one of the following treatment arms:

Intervention: Carboprost 250 micrograms by deep intramuscular injection and 1ml placebo by slow intravenous injection.

Control: Oxytocin 10 international units by slow intravenous injection and 1ml placebo by deep intramuscular injection.

10.2 Formulation, Packaging, Labelling, Storage and Stability

10.2.1 Formulation

COPE trial active treatments (carboprost and oxytocin) are market-authorised drugs being used within the terms of their marketing authorisation. The formulations will be used in their marketed form and will not be manipulated other than over-labelling and packaging as described below.

10.2.1.1 Carboprost

Active carboprost 250 micrograms (Pfizer Limited) is presented as 1ml of a colourless, sterile, aqueous solution for intramuscular injection.

10.2.1.2 Oxytocin

Active oxytocin 10 international units (Hameln Pharmaceuticals Ltd) is presented as 1ml of a colourless, sterile, aqueous solution for infusion.

10.2.1.3 Placebo

The matching placebo is presented as 0.9% Sodium Chloride in 1ml colourless, sterile, aqueous solution for intramuscular injection or for infusion.

10.2.2 Packaging and Labelling

IMP supplies will be secured via Sharp Clinical Services (UK) Ltd, who will procure, over-label and package into blinded treatment kits in accordance with regulation 46 SI 2004/1031 and the detailed guidance provided in annex 13 of the EU Good Manufacturing Practice (GMP) guide. Kits will be sequentially numbered and their number will become the participant's randomisation number.

Each kit will contain two ampoules in an outer carton. Both ampoules and the outer carton will be labelled. Each ampoule is intended for a single dose for a single participant.

10.2.3 Storage and Stability

Treatment kits will be temperature monitored whilst stored at the central manufacturing facility and during shipment to participating centres. Treatment kits will be received and stored by the site pharmacy prior to being dispensed in batches to the participating department where they will be stored until administration in an appropriate, secure refrigerator or in a designated appropriately labelled compartment. The fridge temperature should be maintained at 2-8 degrees Celsius. Kits should not be frozen and ampoules should be kept in their outer carton until required.

The temperature of storage locations will be monitored and documented daily in the temperature log. In the event of storage temperatures falling outside the 2-8 degrees Celsius range permitted, stock should be quarantined and the trial coordinator at the CTRC contacted for further actions.

10.3 Dispensing, Dosage and Administration of Study Treatment/s

10.3.1 Dispensing

IMPs will be supplied as bulk stock from the distributor to pharmacy in kits containing two ampoules.

Authorised, trial-trained pharmacy staff should dispense sufficient kits to the designated recruitment location(s) where they should be stored in accordance with section 10.2.

Pharmacy staff at site will sign and date an accountability log documenting receipt of IMP and recording the dispensed location.

10.3.2 Dosage and Administration

Study interventions are supplied as ready-for-use formulations as a single dose for a single participant. Both ampoules in each kit should be administered at randomisation in accordance with the respective Summary of Product Characteristics (SPC) accessed via the electronic medicines compendium (eMC):

- 1 millilitre Carboprost 250 micrograms by deep intramuscular injection (Pfizer Limited; Hemabate Sterile Solution) and 1 millilitre placebo by slow intravenous injection
  OR
- 1 millilitre Oxytocin 10 international units by slow intravenous injection (Hameln Pharmaceuticals Ltd; Oxytocin 10 IU/ml Concentrate for Solution for Infusion) and 1 millilitre placebo by deep intramuscular injection

As far as packaging allows, **both** ampoules should be visually inspected for particulate matter and discoloration prior to administration. Should this be observed, the whole kit (two vials) should be quarantined, segregated from the other IMP and pharmacy notified. If neither vial has been administered the next sequential kit may be selected to administer COPE treatment. If one vial has already been administered and a problem is noted with the second vial a further COPE kit **should not** be selected. Care should continue as if both vials had been

administered, with the use of the emergency procedures and / or unblinding as required. Both vials should be quarantined, segregated from the other IMP and pharmacy notified.

The quarantined kit/s should be returned to pharmacy as soon as they are next open to await further instruction (pharmacy staff will liaise with CTRC).

Once the IMP is administered treating clinicians will be asked to avoid additional pharmacological interventions for 15 minutes. This time represents the half-life of intravenous oxytocin, and is the time interval specified for repeat doses of carboprost. After this time interval, clinicians will continue with treatment according to NICE guidance and local practice, including the use of further oxytocin or carboprost. Subsequent treatments and actions will be recorded.

10.4 Dose Modifications

Both of the ready-for-use formulations contained within the ampoules in a kit should be administered so that all participants are administered a deep intramuscular injection and a slow intravenous injection. Given the nature of the interventions in this protocol it is not anticipated a modification in dose will be required or feasible.

If a woman continues to bleed heavily after both of the ampoules in the kit have been administered, the managing clinician may wish to instigate additional treatment before the 15-minute threshold is reached. Further management should be conducted in accordance with NICE guidance for the management of PPH.

Guidance on management will be supplied with the treatment kits:

- Clinicians are encouraged to wait for 15 minutes after giving the study drugs before giving any further carboprost or oxytocin bolus.
- If bleeding continues and it is considered necessary to intervene before this, several options are possible:
  PHYSICAL
  - Empty the bladder, massage the uterus and check for genital tract trauma;
  - Put the baby to the breast to stimulate natural oxytocin release;
  - Use bimanual compression, or aortic compression.

  DRUGS
  - Administer face mask oxygen;
  - Give ergometrine (if not hypertensive);
  - Start an oxytocin infusion;
  - Administer intravenous tranexamic acid 1g; or
  - Give misoprostol 800 micrograms sublingual or per rectum.

If, as a last resort, unblinding is necessary, this will be conducted in accordance with section 10.8.

10.5 Overdose

As part of the COPE protocol women will be administered a single dose of carboprost or oxytocin that are each within the parameters of the dose advised in their respective SPC. If administered in accordance with the relevant SPC and this protocol, overdose is unlikely. In the event that overdose is suspected, treatment should be symptomatic and supportive (see also Section 10.7.1 and 11.11).

Suspected overdose should be immediately (within 24 hours) reported to CTRC using the SAE CRF and a root cause investigation should be initiated by the site.

10.6 Delivery and Accountability of IMP at Trial Sites

10.6.1 Delivery

Trial IMP will only be delivered to an investigator site once the site has been initiated by CTRC, acting on behalf of Sponsor to ensure full ethical and regulatory approvals have been granted. The size of the shipments to each site will be pre-determined based on the participant recruitment target for that individual site.

Recruitment will be monitored centrally and drug shipment dates will be tailored accordingly to ensure that pharmacies hold adequate supplies of trial treatment. Pharmacies must document all shipment receipts and will provide copies of this documentation to the CTRC.

IMP stock must be received by a designated member of the pharmacy department and must be stored at 2-8 degrees celsius with temperature monitoring as described in section 10.2.3.

10.6.2 Accountability Procedures for Study Treatment/s

Drug accountability logs will be maintained throughout (accountability and temperature monitoring records will be maintained in the receiving department within site as well as within pharmacy).

Records of all shipments must be kept in the drug accountability log.

If IMP stock received from the distributor is unexpected, wrong, damaged or out of temperature range, the stock should be quarantined and CTRC contacted for further actions.

10.6.3 Expired and unused IMP stock

Any stock that has expired at the trial site during the trial and any stock remaining at trial closedown must be notified to the CTRC, who will authorise destruction. Stock will be destroyed locally according to site policy and records made in the drug accountability log.

10.7 Concomitant Medications/Treatments

10.7.1 Medications Permitted/Not Permitted/ Precautions Required

Once the IMP is administered doctors will be asked to avoid additional uterotonic treatment for 15 minutes. After that, ongoing treatment will be at the discretion of the treating physician and in accordance with NICE guidance and local policies, including the use of further

oxytocin (no more than 10 additional units applied as a bolus) or carboprost (no more than 7 additional doses) (see also section 10.4). In case additional treatment is required it should be assumed that the participant has received either of the randomised treatments oxytocin or carboprost.

10.7.2 Data on Concomitant Medication

Data on concomitant medications will be not be recorded for drugs other than those meeting the criteria below. The drug, reason for use, route of administration, dose and dose duration will be recorded for the below:

- Concomitant medication implicated in an interaction with trial treatment and resulting in a Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR);
- Additional uterotonic use before and after the IMP;
- Blood products;
- PPH prophylactics given;
- Intrapartum oxytocin infusion used.

10.8 Unblinding

Unblinding pressure-sealed envelopes are to be provided to each site by CTRC. They are to be stored in a secure location accessible to trial staff, for example in a controlled drug cabinet. These are to be used to unblind the participant in the event of emergency, when further treatment is considered.

If unblinding is considered appropriate, the unblinding envelope with the randomisation number matching the participant's randomisation number should be accessed ideally after discussing with the original prescriber or if not available with a delegated member of the research team, ideally a prescriber. Following on, CTRC should be informed initially by telephone, and then by completion and return of an unblinding CRF (see also Section 7.5).

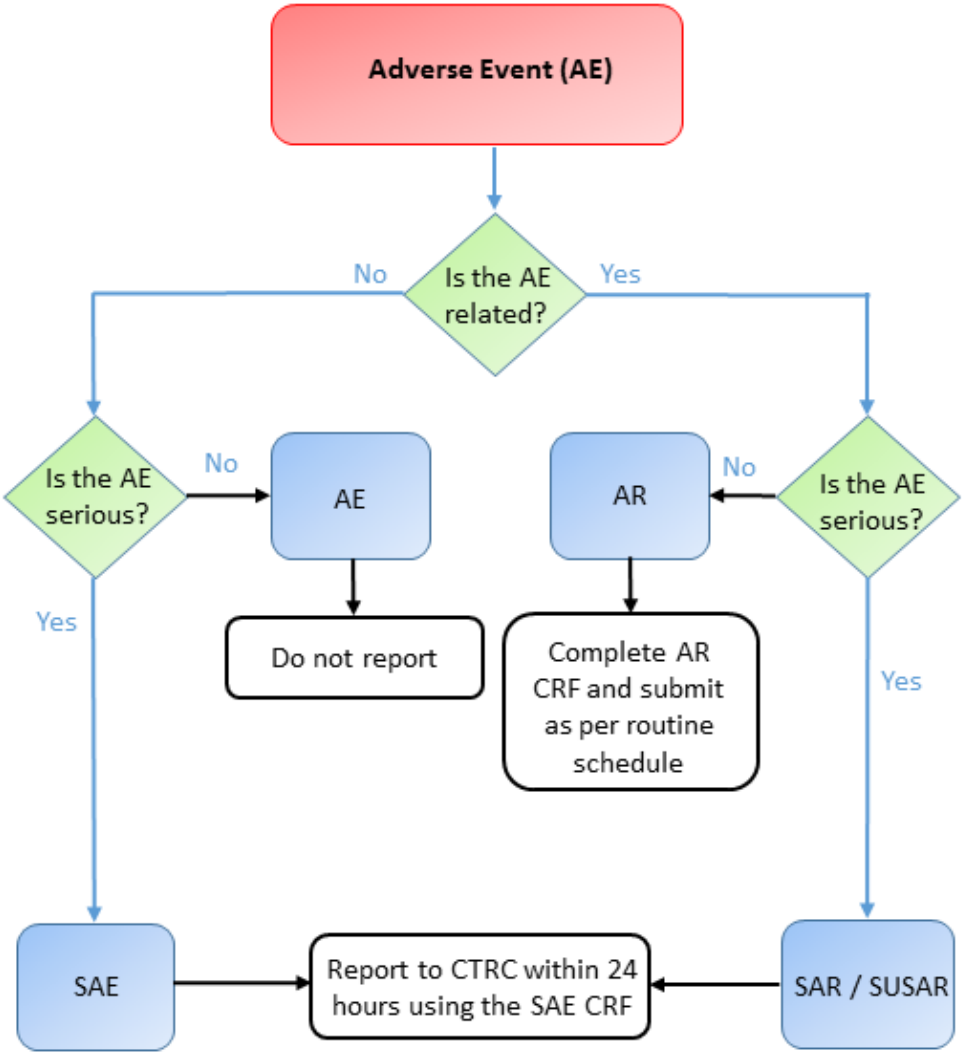
11 SAFETY REPORTING

11.1 Time Period for Safety Reporting

Safety reporting of Serious Adverse Events and non-serious adverse reactions (safety reports that do not meet the “serious” criteria and are considered to be “possibly”, “probably”, or “almost certainly” related to the randomised treatment) will be actively monitored and reported during the clinical trial from the time of randomisation until hospital discharge or 4 weeks, whichever is sooner.

Non-serious adverse events (safety reports that are considered to be “unlikely” to be or “unrelated” to the randomised treatment) do not require reporting.

Figure 4: Flowchart for Reporting Requirements of Adverse Events



11.2 Terms and Definitions

"Adverse Event (AE)"
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Therefore an AE is any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a subject to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product.

"Adverse Reaction (AR)"
Any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject.

Therefore an AR is any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a subject to an IMP which is related to any dose administered to that subject.

"Unexpected Adverse Reaction (UAR)"
An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigator's brochure or the SPC, which may be referenced where the IMP in question is a product with a marketing authorisation.

"Serious Adverse Event (SAE), "Serious Adverse Reaction, or Unexpected Serious Adverse Reaction"
An adverse event, adverse reaction or unexpected adverse reaction respectively that:

- results in death;
- is life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have caused death);
- requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation; hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute a SAE).
- results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis;
- other important medical events (these may not result in death, be life-threatening, or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

"Suspected Serious Adverse Reaction (SSAR)"
An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the case of a licensed product, in the SPC for that product in the case of any other IMP, in the Investigator's Brochure (IB) relating to the trial in question.

"Suspected Unexpected Serious Adverse Reaction (SUSAR)"

An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information.

"Reference Safety Information (RSI)"
The information used for assessing whether an adverse reaction is expected. This is contained in either the IB or the SPC

11.3 Notes on Adverse Reaction Inclusions and Exclusions

For the purpose of pharmacovigilance reporting in COPE, all SAEs will be reported for the duration described in section 11.1.
Only those AEs for which the causal relationship to the randomised study drug is assessed by the investigator as "possible", "probable", or "almost certainly", is classed as an Adverse Reaction (AR) and is reportable for COPE (see section 11.8 for how to report).

11.3.1 Reference Safety Information

The Reference Safety Information (RSI) is the information used for assessing whether an adverse event is an expected reaction.

The RSI in COPE is section 4.8 of respective SPC:
Oxytocin - Oxytocin 10 IU/ml Concentrate for Solution for Infusion, Hameln Pharmaceuticals Ltd
Carboprost - Hemabate Sterile Solution, Pfizer Limited

11.3.2 Include

Include the following only if they are possibly, probably or almost certainly related to the trial treatment:

- An exacerbation of a pre-existing illness;
- An increase in frequency or intensity of a pre-existing episodic event/condition;
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration;
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment;
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event);

- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention;
- Injury or accidents.

11.3.3 Do Not Include

- Any AE whose causal relationship to the trial treatment is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial treatment;
- Medical or surgical procedures;
- Pre-existing disease or conditions present before treatment that do not worsen;
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery;

11.3.4 Notification of deaths

All deaths in participants from the time of randomisation until hospital discharge or 4 weeks, whichever is earlier, should be reported to the CTRC using the SAE CRF **within 24 hours** of the clinical research team becoming aware of the event.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE CRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a participant with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the participant was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the SAE CRF. If the cause of death subsequently becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

11.4 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AR as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe ARs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 11.2, hence, a severe AR need not necessarily be a Serious Adverse Reaction.

11.5 Relationship to Trial Treatment

An assessment of the causality will be made by the investigator responsible for the care of the participant using the definitions in Table 1.

If any doubt about the causality exists, the local investigator should inform the CTRC who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the Medicines for Healthcare products Regulatory Agency (MHRA) will be informed of both points of view.

Table 1: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

11.6 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "almost certainly" is an Adverse Reaction.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as **serious** and **unexpected** (see section 11.3) should be reported as a **SUSAR**.

11.7 Follow-up After Adverse Reactions

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

When reporting SAE, SAR or SUSAR the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

11.8 Reporting Procedures

All SAEs and adverse reactions (AR) should be reported for the duration described in section 11.1. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse reaction reporting should be directed to the CTRC in the first instance. A flowchart is given (Figure 4: Flowchart for Reporting Requirements of Adverse Events) to aid in determining reporting requirements.

11.8.1 Non serious AEs

These events are not reportable for the purposes of COPE pharmacovigilance.

11.8.2 Non serious ARs

All such events, whether expected or not, should be recorded on an Adverse Reaction CRF, which should be transmitted to the CTRC within seven days of the form being completed.

11.8.3 SAEs/ SARs/ SUSARs

All SAEs, SARs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE CRF asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The CTRC will notify the MHRA and REC of all SUSARs occurring during the study according to the following expedited timelines; fatal and life-threatening events within 7 days of notification and non-life threatening events within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and/or SAEs as required locally.

11.9 Responsibilities – Investigator

The Investigator is responsible for reporting all SAEs, and all ARs that are observed or reported during the study and fulfil the criteria listed in Section 11.3.

- All non-serious ARs should be reported on the AR CRF and returned to the CTRC within 7 days.
- All SAEs, SARs and SUSARs must be reported immediately (and no later than 24 hours of becoming aware) by the investigator to the CTRC on a SAE CRF.
- All deaths and overdoses should be reported as described in sections 11.3.4 and 11.11 respectively.

Minimum information required for reporting (CT-3)*

- Valid EudraCT number (if applicable)
- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name- code)
- A causality assessment

i. The SAE form should be completed by a designated investigator, a physician named on the 'delegation of authority and signature log' as responsible for safety reporting and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to an IMP. In the absence of the designated investigator the SAE form should be completed and signed by an alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE form to the CTRC, research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 795 8760** to advise that a SAE form has been submitted. The CTRC trial team should ensure that the number to be used to report SAEs in this way is manned during office hours, and is notified to research site personnel during the site initiation process.

iii. The SAE CRF should be sent by fax (within 24 hours) to the CTRC:

Fax Number: 0151 795 8770

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment, if necessary. A final report will always be expected.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vii. The participant **must** be identified by trial number, date of birth and initials only. The participant's name **must not** be used on any correspondence.

Patient safety incidents that take place in the course of research should be reported locally by each participating NHS Trust in accordance with Trust reporting procedures.

11.9.1 Maintenance of Blinding

Systems for SUSAR and SAE reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding

of clinicians may be unavoidable if the information is necessary for the medical management of particular participant. The safety of participant in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled (section 7.5) and unblinding has taken place. Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at CTRC prior to reporting to the MHRA.

11.10 Responsibilities – CTRC

The CTRC is undertaking duties delegated by the trial Sponsor, the University of Liverpool, and is responsible for the reporting of SAEs, SARs and SUSARs to the regulatory authorities (MHRA and REC) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) and SAEs must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important.
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the CTRC/Sponsor.
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the participants, such as:
    a. A SAR which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the IDSMC, if any, where relevant for the safety of the participants.

Staff at the CTRC will liaise with the Chief Investigator (or designated other specified in the protocol) who will review all SAEs received for seriousness and causality, and assess expectedness. Investigator reports of SAEs will be reviewed immediately and those that are SUSARs identified and reported to MHRA and REC. The causality assessment given by the

Local Investigator at the hospital cannot be downgraded and in the case of disagreement, both opinions will be provided with the report.

The PIs at all institutions participating in the trial will be notified of any SUSARs.

11.11 Overdose

If overdose occurred with resulting signs and symptoms that meet the protocol criteria for AR, SAE, SAR or SUSAR then they should be reported accordingly.

Although overdose of medication without signs or symptoms may be excluded from AE reporting this may still require investigation to ensure the protocol and regulatory requirements are met e.g. for IMP management and administration to ensure participant safety. Therefore, in such circumstances site should immediately (within 24 hours) using the SAE form report to CTRC and a root cause investigation should be initiated.

11.12 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and AR reporting rates across sites. The CTRC will send annual developmental safety update reports (DSUR) to MHRA and REC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC to carry out site visits if there is suspicion of unreported SAEs/ ARs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

11.13 Urgent Safety Measures

An urgent safety measure (USM) is a procedure not defined by the protocol, which is put in place prior to authorisation by the MHRA and REC in order to protect clinical trial participants from any immediate hazard to their health and safety.

The CTRC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the MHRA and REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

If the study is temporarily halted it may not recommence until authorised to do so by the MHRA and REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to MHRA and REC), the sponsor should notify the MHRA and REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

11.14 Out-of-hours Medical Cover

Out-of-hours medical cover will use the standard out-of-hours care available within the hospital.

12 STATISTICAL CONSIDERATIONS

12.1 Introduction

A full and detailed statistical analysis plan (SAP), following ICH E9 and the CONSORT guidelines, will be developed prior to the first comparative monitoring report to be presented to the IDSMC (20). The main features of these planned statistical analyses are detailed below.

12.2 Method of Randomisation

The randomisation list will be generated by a statistician at the CTRC (independent to the COPE trial). Sequentially numbered treatment kits, detailing the randomisation number, will be stored in a secure location in the delivery suite. Upon randomisation the research team will select the next sequentially numbered kit.

Participants will be randomised to carboprost or oxytocin in a 1:1 ratio.

12.3 Sample Size calculation

To detect a 2.3% reduction in a 5.8% transfusion rate (relative risk 0.60) using a Fishers exact test with 90% power (alpha 0.05), we would require 1,880 participants per group, increasing to 3,948 allowing for 5% loss to follow-up.

The magnitude of treatment effect for the primary outcome is needed in order to change long established clinical practice, and to represent a significant advantage, given the carboprost cost and side effects.

Data from sites and published literature provide a range of transfusion rates, the variation of which may be explained by the time point of randomisation. The table below demonstrates the impact of varying the event rate within this range on the study power, all other parameters including the relative effect size are maintained. Therefore, even if the transfusion rate was the lowest observed the study would still have good power. However, the most relevant and accurate data is from the Liverpool audit and we have based our sample size calculations accordingly.

It is planned to recruit equal numbers of caesarean and vaginal births to ensure that study results are convincing across both subgroups. This is to ensure that the study has the potential to impact clinical practice across both modes of delivery. Within each subgroup we would be able to detect a decrease in transfusion rate from 5.8% to 3.0% with 85% power (alpha=0.05, fishers exact test).

Transfusion rate (%)	Power (%)
3.5	71
4.0	77
5.8	90
7.5	96
10	99
Relative effect size 0.60, alpha=0.05, fishers exact test	

Repeat uterotonic is an important secondary outcome and this sample size will provide 87% power, using a chi-square test, to detect a 4.2% reduction from a control group rate of 23.7%.

12.3.1 Feasibility (attaining recruitment targets)

There will be an internal pilot after 6 months, using data from the first five hospitals to open. The rates of recruitment (taking into account the ratio of vaginal to caesarean births), consent, data completeness and sample size assumptions will be assessed.

In order to continue to the main trial, certain criteria should be satisfied as specified in section 4.

12.4 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data, overall and split by delivery method, will be performed at regular intervals (at least annually) for review by the IDSMC. These analyses will be performed at the CTRC. The IDSMC will be asked to give advice to the Trial Steering Committee (TSC) and Trial Management Group (TMG) on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

12.5 Analysis Plan

The primary analysis will follow the intention to treat principle as far as practically possible, such that for all women for whom the outcome is known will be included in their randomly allocated group regardless of intervention received. All analyses will be conducted using a 5% two-sided level of statistical significance and 95% confidence intervals throughout.

The primary analysis will include women from both vaginal and caesarean section deliveries. Fisher's exact test will be used to determine statistical significance as specified within the sample size calculation for the primary outcome with the chi-square or Fisher's exact test used as appropriate for other binary secondary outcomes. Logistic regression will be used to adjust for known prognostic indicators (listed below and subject to blind review at data base lock) and explore interaction between method of delivery and treatment group. Linear regression will be used for continuous secondary outcomes.

The following covariates will be included within the regression models: treatment group; caesarean section or vaginal birth; prophylaxis with oxytocin alone, oxytocin/ergometrine, or none; use of oxytocin for induction/augmentation or not; and retained placenta or not at time of IMP administration.

Baseline characteristics will be presented using descriptive statistics only; there will be no statistical tests between randomised groups.

Adverse Reactions (ARs) and Serious Adverse Reactions/Suspected Unexpected Serious Adverse Reactions (SARs/SUSARs) will also be presented using descriptive statistics only.

12.5.1 Health Economic Analysis.

Total costs from the perspective of the NHS and Personal Social Services will be combined with the measure of health outcome to calculate the incremental cost-effectiveness (utility) ratios (ICER) of carboprost vs oxytocin. Where appropriate, missing resource use or health outcome data will be imputed. The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule, and corrected for 24-hour measurement. We will employ parametric approaches for analysing cost and QALY data that assume normal distributions given the large samples where the near-normality of sample means is approximated. Stratified cost-effectiveness analyses will be conducted on important, pre-specified patient subgroups. Estimates of Incremental cost-effectiveness ratios (ICERs) will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness specified by NICE, and a range of sensitivity analyses will be conducted to assess the robustness of the analysis. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

A full Health Economics Analysis Plan will be completed prior to conducting the analysis.

12.5.2 Qualitative data analysis.

Interviews and audio recordings will be transcribed, checked and anonymised as the study progresses. Qualitative researchers will lead the analysis of data. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Framework analysis will be used to assist the management and interpretation of data (21). The focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and trial recruitment practice (22, 23).

13 REGULATORY AND ETHICAL APPROVALS

13.1 Statement of Compliance

Statement of compliance: The study will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (1996)
- CTRC SOPs
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) (24)
- UK Policy Framework for Health and Social Care Research 2017.
- Medicines for Human use (Clinical Trials) Regulations 2004 (as amended)

13.2 Regulatory Approval

This trial falls within the remit of applicable trials legislation. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The EudraCT number and CTA reference is displayed on the protocol cover page.

13.3 Ethical Approval

The trial protocol has received the favourable opinion of the Research Ethics Committee (REC) but must undergo independent review by the Health Research Authority and capacity and capability assessment at the R&D offices at participating sites.

13.3.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and subsequent revisions from 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Republic of South Africa).

Two key ethical issues have been identified in COPE and our approach has been informed by our Patient & Public Involvement (PPI) activities. These are the consent process and the giving of a placebo intramuscular injection to those allocated to the active oxytocin arm or a placebo intravenous injection for those allocated to the active carboprost.

We have undertaken discussions with consumers on the use of placebo injections. These discussions support our study design with a clear consumer preference to the use of a placebo injection to increase the reliability of the answer to the research question. The approaches undertaken are compliant with the required regulations and national guidelines, and fully justifiable. We therefore are cognisant of these issues but believe that the approaches will not raise ethical concerns.

Consent procedures for this emergency study follow the recommendations of consumer groups, the Royal Colleges and are in compliance with ethical and regulatory frameworks. Information about the study will be distributed to target women during pregnancy through posters, leaflets, websites and on social media. As described in section 7.3, those women who bleed after childbirth and meet the eligibility criteria will be randomised into the trial in the emergency situation where treatment needs to be given urgently and there is no time for

prior consent. There will also be the opportunity for prior consent for those at high risk. This approach has been successfully used in several recent trials of emergencies in labour (6, 8, 9).

13.4 Health Research Authority (HRA) Approval

In order for the study to take place within NHS an approval from the Health Research Authority (HRA) will be required. This is coordinated by CTRC.

13.4.1 Capacity and capability assessment

The local Research & Development (R&D) offices should be sent the appropriate site-specific information packs complete with the necessary authorisation signatures, plus any other documentation requested for review. This review can take place at the same time as the HRA review. A copy of local R&D capacity and capability assessment should be forwarded to CTRC before the site is initiated and patients recruited.

13.5 Protocol Deviation and Serious Breaches

A breach of the protocol or GCP is 'serious' if it meets the regulatory definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". All serious breaches of GCP or protocol will be reported to the MHRA and REC in an expedited manner by the CTRC.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the CTRC who will in turn notify the sponsor. The sponsor will assess the breach and determine if is meets the criteria of a 'serious' breach of GCP or protocol and therefore requires expedited reporting to the MHRA and REC.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC). In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice form the Trial Statistician. However, the sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to the MHRA and REC within 7 days by the CTRC and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the sponsor, TMG, TSC, IDSMC, REC or MHRA, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidence of protocol non-compliance are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

13.6 Study Discontinuation

In the event that the study is discontinued, participating sites will be advised on any actions that are required with regards to individual participants follow-up.

Participants will otherwise be treated according to the usual standard clinical care. The process for participants who withdraw early from trial is described in section 8.5.

14 DATA MANAGEMENT AND TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial. Monitoring can take the form of on-site visits or central monitoring. A detailed monitoring plan will be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

Details of the monitoring to be carried out for the COPE study are included in the COPE Trial Monitoring Plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.4.

14.1 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the case report form (CRF) and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.

The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF. A COPE source document list will be completed by each site.

Date(s) of conducting informed consent process including date of provision of patient information, randomisation number, confirmation of full eligibility by an authorised medical doctor, and the fact that the patient is participating in a clinical trial should be added to the patient's medical record chronologically.

14.2 Data Capture Methods

The study case report form (CRF) is the primary data collection instrument for the study. Guidelines regarding data collection requirements, CRF completion and responding to data queries will be provided to sites.

14.3 Monitoring

14.3.1 Central Monitoring

Data stored at CTRC will be checked in accordance with data management and monitoring SOPs. Data clarification forms will be produced and provided to a named individual at a site (as listed on the site delegation log) in order to query data. Returned data clarification forms are filed along with the relevant CRFs after the appropriate corrections made on the database. There are a number of monitoring features in place at the CTRC, detailed in the trial monitoring plan, to ensure reliability and validity of the trial data.

14.3.2 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or other CTRC personnel) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

14.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited without prior agreement in accordance with the Common Law Duty of Confidentiality. Agreement will be achieved during the trial consent process for disclosure by the clinical care staff to the COPE research team, and for sharing of information between the COPE team and NHS Digital and devolved nation equivalents. Medical information may also be given to the participant's wider medical team and all appropriate medical personnel responsible for the participant's welfare.

Data processing will be performed in accordance with applicable data protection legislation. The University of Liverpool is registered with the Information Commissioner's Office; as Data Controller for this study, the University of Liverpool will process data under the legal basis of performing a task in the public interest for research purposes.

The CTRC will be undertaking activities requiring the transfer of personal identifiers (e.g. name):

- Verification that appropriate informed consent for trial participation is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the CTRC by recruiting centres, which requires that name data will be transferred to the CTRC.
- Obtaining medical data from NHS Digital and devolved nation equivalents will require CTRC to collect NHS (or CHI) numbers and transfer them to the applicable organisations.

This transfer of identifiable data is disclosed in the Patient Information Sheet.

With the exception of the trial consent form, all other CRFs will be pseudonymised: labelled with the participant's initials and unique trial randomisation number, except for the eligibility CRF, which will use participant's screening number.
Sites must ensure other trial documents are not posted in the same envelope as the consent form as there is a risk to patient confidentiality.

14.4.1 Hospital Episode Statistics (HES)

To obtain HES data and SMR data from NHS Digital, the NHS Wales Informatics Service information Centre and the electronic Data Research and Innovation Service, identifiable patient information will be transferred from CTRC to these NHS organisations as per section 8.4.2. This transfer is going to be disclosed in the trial patient information sheet and consent.

14.5 Quality Assurance and Control

Quality Assurance (QA) includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality Control (QC) includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled e.g. state what clinical site monitoring (and audit) is planned, if any. In accordance with the monitoring plan site visits will or will not be conducted and source verification performed, if indicated to be require as a result of central monitoring processes.

- The Trial Coordinator at the CTRC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at CTRC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated and will monitor screening, randomisation and consent rates between centres.
- Independent oversight of the trial will be provided by the IDSMC and independent members of the TSC.
- The PI and other key staff from each centre will attend site initiation training, coordinated by the CTRC, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with CTRC SOPs.

14.6 Records Retention

(ICH GCP 4.9.5) "Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no ending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained".

The COPE trial's essential documents (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) will be retained for 25 years following the End of Trial.

The PI at each investigational site must make arrangements to store the site-specific essential trial documents including the Investigator Site File and Pharmacy Site File, until the CTRC informs the investigator that the documents are no longer to be retained.

The PI is also responsible for ensuring archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).
The PI is required to ensure the continued storage of the documents, even if she/he leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTRC will archive the documents in compliance with GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long-term accessible storage. Hard copies of data will be boxed and transferred to, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 INDEMNITY

COPE is sponsored by the University of Liverpool and co-ordinated by the CTRC in the University of Liverpool. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of clinical research, including but not limited to the authorship of the Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
“A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.

16 ROLES AND RESPONSIBILITIES

16.1 Role of Study Sponsor and Study Funder

This study is funded by the Health Technology Assessment programme of National Institute for Health Research (HTA NIHR) and sponsored by the University of Liverpool. The sponsor's roles and responsibilities are outlined in the COPE collaborators agreement.

16.2 Funding and Support in Kind

Contractual agreements will be in place between sponsor and participating centres that will describe financial arrangements.

Table 2: Study Funder

Funder(s)	**Financial and Non-financial Support Given**	**Role**
NIHR HTA	Financial support is described in the main contract. NIHR HTA provides on-going help and support to the CI to ensure that the project progresses smoothly. Trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results are the responsibility of sponsor and their delegates, though the funder will monitor progress against key milestones via the submission of regular progress reports. The funder requires to approve the initial protocol and amendments prior to submission for ethical/regulatory approval. The funder requires to be provided with copies of project outputs at least 28 days before publication or presentation.	Funder

16.2.1 NHS Research costs

16.2.1.1 Per site

To reflect site personnel time on the study to fulfil the needs of the research, e.g. preparing for an attending initiation/ monitoring meetings, a per-site payment is included in the budget and detailed in the contract between sponsor and site.

16.2.1.2 Per patient recruited

Research related activity, including data collection, will be supported by a per-patient payment. In COPE the patient care pathway mirrors usual care in this acute emergency situation and data collection forms will be formatted to ensure that critical variables can be collected in the busy emergency setting. However in order to support the robust recruitment and follow-up of participants a per-patient payment is budgeted and detailed in contracts. The per-patient payment for transferred participants will be given to the recruiting hospital (see section 8.5.3).

16.2.2 NHS Support costs

This trial will be entered into the NIHR CRN portfolio and infrastructure support will be available through the CRN network.

16.2.3 Treatment costs

Study treatments will be supplied to participating sites by a central manufacturing facility.

16.3 Protocol Contributors

Name	Affiliations (organisation address)	Contribution to protocol
Professor Andrew Weeks	Sanyu Research Unit, University of Liverpool	Clinical aspects, trial design and conduct
Dr Shireen Meher	Birmingham Women's Hospital	Clinical aspects, trial design and conduct
Helen Hickey	Clinical Trials Research Centre, University of Liverpool	Governance arrangements and trial design and conduct
Carrol Gamble	Clinical Trials Research Centre, University of Liverpool	Statistical lead in trial design and conduct including monitoring, and analysis
Charlotte Van Netten	Clinical Trials Research Centre, University of Liverpool	Governance arrangements and trial conduct
Katie Neville	Clinical Trials Research Centre, University of Liverpool	QA oversight
Kerry Woolfall	University of Liverpool	Embedded study design and trial consent process
Louise Roper	University of Liverpool	Embedded study design and trial consent process

Clare Jackson	Clinical Trials Research Centre, University of Liverpool	Data Management and trial monitoring oversight
Sylvia Balabanova	Clinical Trials Research Centre, University of Liverpool	Governance arrangements and trial conduct
Catrin Plumpton	University of Bangor	Health Economics
Anna Rosala-Hallas	Clinical Trials Research Centre, University of Liverpool	Statistical analyses under the supervision of the statistical team leader

16.4 TRIAL COMMITTEES

16.4.1 Trial Management Group (TMG)

A TMG will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC. The TMG will meet regularly and is responsible for the day-to-day running and management of the trial. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.4.2 Trial Steering Committee (TSC)

The TSC will consist of an independent chairperson, independent experts in the field of clinical obstetrics and a biostatistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.4.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent chairperson, plus 2 independent members: one who is an expert in the field of obstetrics, and one who is an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually).

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

17 PUBLICATION AND DISSEMINATION

17.1 Publication Policy

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

17.1.1 Authorship

All publications shall include a list of contributors, and if there are named authors, these should include the trial's Chief Investigator, Statistician(s), Health Economist(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

17.2 Dissemination to Key Stakeholders

Trial results will be published in highly reputable peer-review journals and disseminated via scientific meetings and conferences, as well as through the trial website and any professional networks. Trial results will be disseminated regardless of the magnitude or direction of effect. The clinical trial report will be submitted within 12 months of the end of trial.

17.3 Data Sharing

Requests for data sharing following trial closure should be made to the sponsor for consideration.

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 1.0 (10/07/2018)

- Original version.

18.2 Version 2.0 (10/09/2018)

- Reference to type A trial removed (Section 11, page 43).
- Inclusion of all serious adverse events to be recorded from the time of randomisation until hospital discharge or 4 weeks, whichever is sooner (Sections 10.7.2 - 11.12, pages 42 - 51).
- Requirement for the investigator to contact the Sponsor before unblinding removed (Sections 10.8 & 11.9.1, pages 42 & 49, respectively).

19 REFERENCES

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APPENDIX 1. COPE OUTCOMES

Objectives	Outcome Measure	Definition, time frame of assessment and procedure (8.2)		Timepoint(s) of data collection
Primary Objective To compare carboprost with oxytocin as initial treatments for women with clinically diagnosed PPH after giving birth in British hospitals.	Primary outcome			
	1. Blood transfusion	Any RBC blood transfusion or cell salvage of ≥ 300mls commenced any time between randomisation and 48 hours after randomisation (or hospital discharge if earlier than 48 hrs)		After hospital discharge
	Secondary outcomes			
	2. Volume of Blood transfusion	Data will be collected on total units of blood transfusion given, from randomisation up to 48 hrs (or hospital discharge if earlier).		After hospital discharge
	3. Use of a further uterotonic drug	Use of any uterotonic agent additional to IMP administered to control ongoing bleeding, from time of randomisation up to 24 hrs after randomisation.		After hospital discharge
	4. Composite outcome of any organ dysfunction	The composite includes any woman who develops one or more of the following from randomisation up to hospital discharge or 4 weeks, whichever is earlier. Composite based on the definitions used in the WHO Near-miss approach for maternal health' (2). Each of the items will also be reported separately.		After hospital discharge or 4 wks, whichever is earlier
		Renal dysfunction		
		Acute renal failure	Dialysis for renal failure or severe acute azotemia: creatinine ≥ 300 µmol/l or ≥ 3.5 mg/dl	
		Oliguria non-responsive to fluids or diuretics:	A urinary output <30 ml/h for 4 hours or <400 ml/24h non-responsive to fluids or diuretics	
		Cardiovascular dysfunction		
		Cardiac arrest	Sudden absence of pulse and loss of consciousness or cardio-pulmonary resuscitation	
		Cardiopulmonary resuscitation	A set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims	

		Use of continuous vasoactive drugs:	The continuous use of any dose of dopamine, epinephrine or norepinephrine. In the context of vasoactive drugs infusion, continuous use refers to the uninterrupted infusion of a solution containing a vasoactive drug. It is opposed to the intermittent or in bolus injection of a vasoactive drug.	
		Persistent shock	Systolic blood pressure <80mmHg that fails to respond to treatment with a fluid challenge	
		Severe hypoperfusion	Lactate >5 mmol/l or 45 mg/dl	
		Severe acidosis	A blood pH <7.1	
		Coagulation/haematologic dysfunction		
		Coagulopathy	Severe Acute thrombocytopenia (<50 000 platelets/ml), low fibrinogen (<100 mg/dl), prolonged prothrombin time (≥1.5x normal), or Fibtem A5 <6mm.	
		Massive transfusion	Transfusion of ≥5 units of blood or red blood cells.	
		Neurologic dysfunction		
		Prolonged unconsciousness	Any loss of consciousness lasting more than 12 hours, involving complete or almost complete lack of responsiveness to external stimuli / Glasgow Coma Scale <10.	
		Stroke	Acute death of brain cells in a localised area due to inadequate blood flow, diagnosed clinically.	
		Uncontrollable fits	Refractory, persistent convulsions. Status epilepticus.	
		Total paralysis	The complete or partial paralysis of both sides of the body. Usually, an extreme neuromuscular global weakness associated with critical illness. This condition is also known as critical illness polyneuromyopathy.	
		Respiratory dysfunction		
		Severe tachypnoea	Respiratory rate of more than 40 breaths per minute.	
		Severe bradypnea	Respiratory rate of less than 6 breaths per minute	
		Severe hypoxemia	Oxygen saturation <90% for ≥60min or PaO_2/FiO_2<200	
		Ventilation	Intubation and ventilation not related to anaesthesia	
		Acute cyanosis	Acute onset of bluish discolouration of mucous membranes and lips	
		Hepatic dysfunction		

		Severe acute hyperbilirubinaemia	Bilirubin >100 umol/L or >6.0 mg/dL	
		Jaundice in the presence of pre-eclampsia	Acute onset yellowish discolouration of skin and sclera occurring in the presence of pre-eclampsia [blood pressure of greater than 140/90mmHg in the presence of proteinuria (+) or more on urinary dipstick or Protein-creatinine ratio > 30mg/mmol)]	
		Hysterectomy	Surgical removal of the uterus to treat postpartum haemorrhage or infection from any time after randomisation up to hospital discharge (or 4 weeks, whichever is earlier).	
	5. Hysterectomy	Surgical removal of the uterus any time after randomisation up to hospital discharge (or 4 weeks, whichever is earlier)		After hospital discharge
	6. Blood loss	Estimated or measured vaginal blood loss in mls commencing in the first 24 hours from randomisation, up to cessation of active bleeding. The estimated blood loss will be recorded, and supported by blood loss collection and / or weighing where possible.		After hospital discharge
	7. Blood loss ≥ 1000 mls	Volume blood loss ≥ 1000 mls		After hospital discharge
	8. Haemoglobin	Postnatal Haemoglobin (Hb) closest to 24 hours after randomisation Hb in non-transfused women-will be ideally obtained postnatally on the day following birth (12-36 hours post-randomisation) or at discharge, whichever is soonest. If repeated Hb measures have been obtained in the 12-36 hour window then the value obtained closest to 24 hours will be used		After hospital discharge,
	9. Shock	The presence of systolic blood pressure <80mmHg within 24 hours of randomisation		After hospital discharge
	10. Maternal death	Death of the mother within 4 weeks of the birth where postpartum haemorrhage was a contributing factor (it does not need to be the primary cause). Data will be collected on all maternal deaths, along with cause of death.		After hospital discharge, and supplemented from Hospital Episode Statistics.
	11. Non pharmacological approach to treat or investigate bleeding	Use of any non-pharmacological approach to treat bleeding, from randomisation up to hospital discharge. Such non-pharmacological interventions include: laparotomy, internal uterine tamponade with balloon or uterine packing, arterial embolization, removal of retained products.		After hospital discharge

	12. Manual removal of placenta	Manual removal of placenta required post randomisation up to hospital discharge.	After hospital discharge
	13. Any adverse reactions of the intervention for the mother	1. Hypotension developed within 2 minutes of IMP administration Adverse reactions as listed below, occurring within 2 hrs of IMP administration: 2. Vomiting 3. Pyrexia; temperature of >38°C 4. Headache 5. Hot flushes 6. Diarrhoea	Throughout
	14. Skin to skin care with baby within the first hour after birth	Where the newborn is placed unwrapped against the mother's bare chest or belly from anytime after randomisation up to 1 hour after birth.	At 24 hrs
	15. Separation from new-born in first hour after birth	Separation of the newborn from the mother post randomisation up to the first hour after birth. .	At 24 hrs
	16. Breastfeeding	'Breastfeeding' refers to feeding of the baby with the mother's breast milk, even if this is expressed breast milk given by cup or bottle	At 24 hrs, 48 hrs (or hospital discharge if sooner) and 4 wks
		Initiation: Breastfeeding initiated within the first 24 hours after birth.	
		Exclusively at hospital discharge: Exclusive breastfeeding at hospital discharge (i.e. no formula milk, other liquids, or food)	
		Exclusively at 4 weeks post-birth: Exclusive breastfeeding at 4 weeks post birth (i.e. no formula milk, other liquids, or food)	
	17. Childbirth experience questionnaire	Questionnaire on childbirth experience administered to women at 4 weeks postnatally.	At 4 wks

Secondary Objective To assess relative cost-effectiveness of use of carboprost or oxytocin as initial treatments for women with clinically diagnosed primary PPH.	18. Resource use	Resource use will include direct costs, and quality-adjusted life-years to estimate the incremental cost effectiveness rate. These will be captured using EQ-5D-5L, resource use questionnaire and hospital episode statistics.	At 24 hrs and 4 wks.
		QUALY measured using EQ-5D-5L	
		Bespoke self-report instrument designed to capture participants' resource use.	
		Electronic data records of hospitalization will be requested from NHS Digital (England) and devolved equivalents, based on NHS Number. **This will include data on transfer to a higher level of care** This is the transfer of the place of care **due to** a postpartum haemorrhage. This refers to any transfer for more specialist care, but examples would be a transfer from home to hospital, from one hospital to another for specialist input, from a high dependency care unit to an intensive care unit, or from a midwifery led unit to an intensive care unit.	Data will be requested following completion of follow-up from NHS Digital.