TRIAL PROTOCOL

SEE U

Surgical Evacuation with intraopErative Ultrasound: a pilot trial to assess feasibility

This protocol has regard for the HRA guidance

Version Number: 2.0

Version Date: 08-Mar-2019

Protocol development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

Funding and Support in Kind	
Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this trial)	**Financial and non-financial support given:**
NIHR	Financial
Funding Scheme (if applicable)	NIHR Fellowship Programme
Funder's reference number	PDF-2015-08-099
Department of Health disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.	

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

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

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

This protocol has been approved by:

Trial Name:	SEE U: Surgical Evacuation with intraopErative Ultrasound
Protocol Version Number:	Version: __. __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
CI Name:	Dr Paul Smith
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor of this trial confirm approval of this protocol.

Reference Numbers	
Sponsor number	RG_17-249
ISRCTN reference number	TBC
IRAS reference number	253447

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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

This protocol has been approved by:

Trial Name:	SEE U: Surgical Evacuation with intraopErative Ultrasound
Protocol Version Number:	Version: __. __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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Trial website	www.birmingham.ac.uk/seeu

ABBREVIATIONS

Abbreviation	Term
BCTU	Birmingham Clinical Trials Unit
ICF	Informed Consent Form
PIS	Participant Information Sheet
REC	Research Ethics Committee
UoB	University of Birmingham

DEFINITIONS

Term	Abbreviation	Description
Policies	POL	Policies are developed to describe the approach of the University of Birmingham UoB on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures

		and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator**
Unexpected and Related		An event which meets the definition

Event		of both an Unexpected Event and a Related Event.
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.
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.
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.

TRIAL SUMMARY

Title: SEE U: Surgical Evacuation with intraopErative Ultrasound

Objectives: To test the premise that intraoperative ultrasound can reduce the incidence of early and late complications following surgical removal of products of conception.

Trial Design: Prospective, pilot, 2 arm, multicentre, randomised, open clinical trial to assess feasibility.

Participant Population and Sample Size: Women aged 16 years or over that are referred for surgical management of miscarriage. The required sample size is 90 patients.

Eligibility Criteria

Inclusion criteria:

- Aged 16 years or over.
- Referred for surgical evacuation of products of conception.
- Willingness to be randomised between treatment modalities.
- Willingness to undergo office hysteroscopy 4-8 weeks after surgical management of miscarriage.
- Written informed consent obtained prior to surgical evacuation.

Exclusion criteria:

- Incomplete or retained products of conception will be excluded from the trial as there are no widely used criteria for deciding which women should have surgical evacuation
- Suspicion of malignant gestational disease.

Intervention: Surgical evacuation of products of conception with intraoperative ultrasonography.

Comparator: Surgical evacuation of products of conception without intraoperative ultrasonography.

Outcome Measures:

Process outcomes

To obtain estimates for important aspects of the protocol to allow development of a substantive trial, specifically:

1. To derive real-time data on the design aspects of the study:
    I. Proportion of eligible women of those screened.
    II. Proportion of eligible women randomised.
    III. Attrition rates (proportion of women followed-up at 2 to 4 and 4 to 8 weeks)
    IV. Proportion of women switching treatments

2. To derive a realistic understanding of trial processes, in particular:
    I. Ascertain robustness of the data collection process during and after the surgical procedure.
    II. Determine the support required in units to ensure successful recruitment
    III. Determine why patients decline participation or withdraw after randomisation.

Evaluation of acceptability to processes and intervention for patients and staff

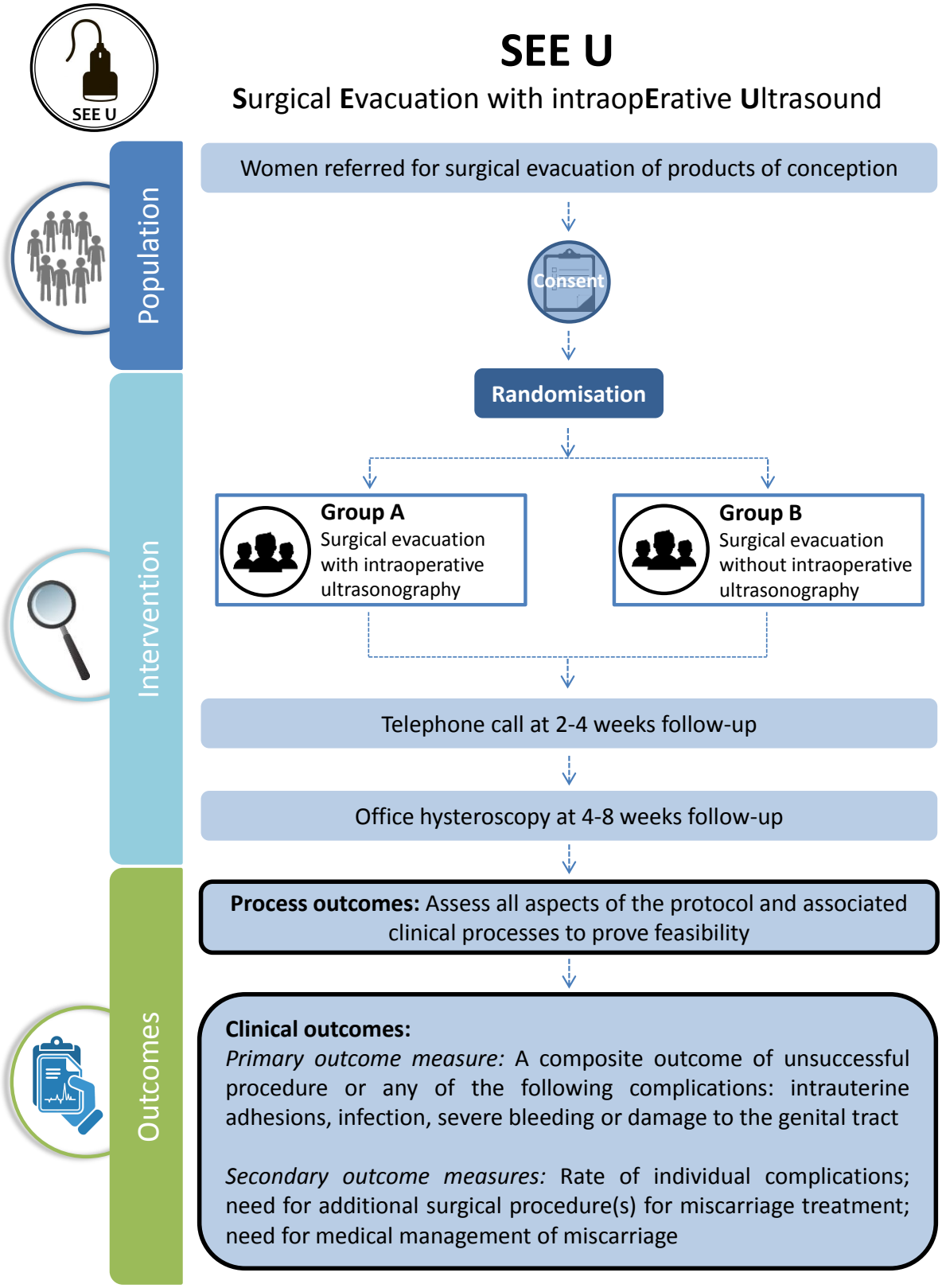
1. Evaluate if outcome measurement tools and processes are acceptable and adequate.
2. Acceptability and impact on patients of the interventions.
3. Assessment of trial processes, including the choice of outcome measures and impact on staff.

Clinical outcomes

Primary outcome measure: A composite outcome of unsuccessful procedure or any of the following complications: intrauterine adhesions, infection, severe bleeding or damage to the genital tract

Secondary outcome measures: Rate of individual complications; rate of serious adverse events; need for additional surgical procedure(s) for miscarriage treatment; need for medical management of miscarriage

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1. Background

First trimester miscarriage occurs in approximately 1 in 9 pregnancies (1). The clinical symptoms of miscarriage are vaginal bleeding usually associated with abdominal pain and cramping. Miscarriage can have serious impacts on the psychological and physical health of both woman and their partners (2–5).

Increasingly, there has been a move to expectant or medical management for early miscarriage because they have been shown to be more cost-effective (6,7). However, expectant and medical management leads to a higher risk of incomplete miscarriage, need for unplanned surgical emptying of the uterus, bleeding and need for blood transfusion, while the risk of infection and psychological outcomes are similar to surgical management (6,7). Current recommendations are for women to be offered an informed choice for expectant, medical or surgical management in pregnancies less than 13 weeks (6,7). Many women prefer surgical management because of the speed and predictability of the process, while others opt for medical or expectant management to avoid more invasive procedures or because they feel these options give them a greater sense of control (8). Therefore, when women make an informed choice surgical management will continue to have an important role. Surgical management is also indicated when medical or expectant management fails or there is heavy bleeding (9).

The surgical management of miscarriage is also known as the evacuation of retained products of conception (ERCP). Traditionally, surgical management of miscarriage was done using a sharp curette but it can also be done using a vacuum device. A Cochrane review comparing the two concluded that vacuum devices were faster, less painful and associated with less blood loss than, and at least as safe, as sharp curettage (10). For this reason suction devices are recommended for surgical management although the technique used is often dependant on the skills and experience of the surgeon. In the UK, surgical management of miscarriage is usually done under regional or general anaesthetic, but it can be done with conscious sedation or local anaesthetic in the office setting with a manual vacuum device (MVA) (11). Although women were shown to return to normal activities quicker with MVA, it was associated with higher pain scores and a trend for decreased acceptability (11). Currently the choice offered to women depends on local services and the experience of the health professionals.

During miscarriage as the uterus is enlarged it is more prone to trauma, which can result in bleeding and perforation. Some of tissues of conception maybe retained and infection can be introduced into the uterine cavity. Both trauma and infection are implicated in the formation of intrauterine adhesions (Asherman's syndrome), which are associated with pain, amenorrhoea, placental implantation problems and decreased fertility.

In an effort to decrease perforation and ensure complete removal of retained products it has been proposed that hysteroscopic techniques can be used. However, hysteroscopic techniques could greatly increase the cost of the procedure and the visual field can be severely compromised when there is heavy bleeding limiting their application to chronically retained products of conception. Another way of visualising the cavity is with ultrasound. With the advent of cheap and portable ultrasound devices, the availability of ultrasound and

the skills needed to perform ultrasound are increasingly being disseminated through the field of gynaecology. Previous work has shown that routine uses of intraoperative ultrasound reduces the incidence of uterine perforation in second trimester abortions (12) and reduces the incidence of infection and repeat treatment in first trimester abortions (13). Therefore, intraoperative ultrasound could also reduce the incidence of the perforation during operative procedures in the treatment of first trimester miscarriage. Furthermore, intraoperative ultrasound can ensure complete removal of products while minimising trauma to the cavity that could cause intrauterine adhesions.

We propose a randomised controlled study to test the premise that intraoperative ultrasound can reduce the incidence of early and late complications following surgical removal of products of conception.

1.2. Trial Rationale

The reasons why this trial is needed are as follows:

1. There are no existing trials looking at the role of abdominal ultrasound in the surgical management of miscarriage.
2. Miscarriage is a highly prevalent condition with substantial morbidity and costs. If benefit is confirmed in a substantive study, women and the NHS stand to gain substantially.
3. Portable ultrasound machines are now readily available in gynaecology units. Therefore the use of a scan during surgical management of miscarriage is cheap and if benefit is confirmed, we expect rapid uptake of this intervention.
4. A UK and International clinician survey supports the study. The study found that 44/68 (65%) thought there was a need for a clinical trial to investigate if performing an abdominal ultrasound during surgical management of miscarriage is beneficial, while 51/68 (75%) said they were willing to participate in the trial.
5. A UK survey of patients also supports the study. The survey showed that 21/25 (84%) said they would consider taking part in the randomised controlled trial.

Therefore, this pilot study will provide us with the preliminary data that can be used to plan the substantive trial.

1.2.1. Justification for participant population

The participant population has been selected because the surgical management of miscarriage remains one of the most common surgical procedures. It is likely to remain an important intervention as current guideline suggest that patient should be offered a choice of conservative, medical or surgical treatment. Moreover, surgical management is needed when conservative or medical treatment fails and when heavy bleeding compromises the patient. Given how common the procedure is even a small reductions in complications could be beneficial to a large number of women.

1.2.2. Justification for design

The design has been selected as a randomised-controlled trial, looking at the effect of ultrasound during the surgical management of miscarriage. There is no evidence to suggest that the addition of ultrasound is inferior to current treatment. An alternative would have been a non-randomised controlled trial, but this cannot rule out the possibility that any significant association was caused by a third factor linked to both ultrasound and complications.

1.2.3. Choice of intervention

To decrease the complications and ensure complete removal of retained products of conception it has been proposed that procedures should be done under vision. Hysteroscopic techniques could be used, but this would greatly increase the cost of the procedure and the visual field can be severely compromised when there is heavy bleeding limiting their application to chronically retained products of conception. Another way of visualising the cavity is with ultrasound. With the advent of cheap and portable ultrasound devices, the availability of ultrasound and the skills needed to perform ultrasound are increasingly being disseminated through the field of gynaecology. Previous work has shown that routine use of intraoperative ultrasound reduces the incidence of uterine perforation in second trimester abortions [12]. Therefore, intraoperative ultrasound could also reduce the incidence of the perforation during operative procedures in the first trimester. Furthermore, intraoperative ultrasound can ensure complete removal of products while minimising trauma to the cavity that could cause intrauterine adhesions.

2. AIMS AND OBJECTIVES

The overall objective is to test the premise that intraoperative ultrasound can reduce the incidence of unsuccessful procedures or early and late complications following surgical removal of products of conception. To answer this question a multi-centre randomised controlled study with an associated health economic evaluation is required.

To ensure the feasibility of a large expensive trial it is essential to perform a pilot study. Performing a pilot study prior to a main study can avoid trials that will fail and increase the likelihood of success of the main study (14).

2.1. Aims and Objectives

The aim of this pilot study is to assess various aspects of the trial design and management and not to determine the relative effectiveness of intraoperative ultrasound during surgical removal of products of conception. The objectives for the pilot study are:

To obtain estimates for important aspects of the protocol to allow development of a substantive trial, specifically:

Process outcomes

1. To derive real-time data on the design aspects of the study:
    I. Proportion of eligible women of those screened.
    II. Proportion of eligible women randomised.
    III. Attrition rates (proportion of women followed-up at 2 to 4 and 4 to 8 weeks)

2. To derive a realistic understanding of trial processes, in particular:
    IV. Ascertain robustness of the data collection process during and after the surgical procedure.
    V. Determine the support required in units to ensure successful recruitment
    VI. Determine why patients decline participation or withdraw after randomisation.

Evaluation of acceptability to processes and intervention for patients and staff

1. Evaluate if outcome measurement tools and processes are acceptable and adequate.
2. Acceptability and impact on patients of the interventions.
3. Assessment of trial processes, including the choice of outcome measures and impact on staff.

Clinical outcomes

1. Derivation of the preliminary data from clinical outcomes measures, in particular intrauterine adhesions at 6 weeks, to inform sample size.
2. Evaluate if outcome measurement tools and processes are acceptable and adequate.

The pilot study should enable us to come to one of the following conclusions:

- A substantive study is not feasible.
- A substantive study is feasible with substantial modifications to the trial protocol to improve recruitment, compliance and follow-up.
- A substantive study is feasible with minor modifications to the trial protocol to improve recruitment, compliance and follow-up.
- The substantive study is feasible using the pilot protocol.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

The trial will be a prospective, pilot, two arm, multicentre, randomised, open clinical trial. The trial will compare surgical evacuation of products of conception with intraoperative ultrasonography versus surgical evacuation without intraoperative ultrasonography. This is a pilot study to optimise study processes and the design of a substantive trial.

3.2. Trial Setting

This pilot study will take place in a minimum of three UK hospitals.

3.3. Identification of participants

The research team will work closely with the multidisciplinary team responsible for routine patient care. The research team will consist of doctors, research nurses and research midwives. All women undergoing a routine (low risk) surgical evacuation of products of conception will be considered for the trial. Their clinical notes will be screened in order to ascertain eligibility. Only a member of the patient's existing clinical care team will have access to patient records in order to identify potential participants and check whether they meet the inclusion criteria or make the initial approach to patients. It is expected that participants will mainly be identified in the early pregnancy units after ultrasound diagnosis of miscarriage and on the emergency gynaecology wards prior to surgical management of miscarriage. The trial will be introduced through a comprehensive, evidence-based patient information sheet that will be provided prior to the procedure. Participant information sheets and consent form will be provided to each centre in English and other languages as appropriate to their local community. All participants will be approached and recruited at a recruiting NHS hospital. A patient facing poster advertising the study will be displayed in clinically appropriate areas within the hospital.

Before the procedure, the women will be given a chance to discuss the risks and benefits of surgical evacuation with or without intraoperative ultrasonography. Written consent will then be obtained prior to randomisation.

3.4. Assessment of Risk

The safety of the ultrasound is well established. The current consensus is there are no negative side effects to the patient if performing diagnostic ultrasound according to current regulatory guidelines (15).

The risks of the surgical management of miscarriage are outlined within the Royal College of Obstetrics and Gynaecology consent for surgical evacuation of the uterus for early pregnancy loss (16). The serious risks include: uterine perforation (5 in 1000 women) which may require laparoscopy or laparotomy to diagnose or treat organ injury; significant trauma to the cervix (1 in 1,000 to 10,000). Frequent risks include: bleeding that lasts for up to two

weeks is very common but bleeding leading to blood transfusion is uncommon (1-2 in 1,000 women); pelvic infection (3 in 100 women); repeat surgical management (5 in 100 women).

The alternatives include medical management with mifepristone and prostaglandins or expectant management, particularly without an intact gestational sac. These alternatives are associated with heavier and longer bleeding and a 15-50% chance of requiring surgical treatment either as an emergency or the woman's preference.

This trial is categorised as:

Type A: No higher than the risk of standard medical care

4. ELIGIBILITY

4.1. Inclusion Criteria

- Aged 16 years or over.
- Referred for surgical evacuation of products of conception.
- Willingness to be randomised between treatment modalities.
- Willingness to undergo office hysteroscopy 4-8 weeks following surgical management of miscarriage.
- Written informed consent obtained prior to surgical evacuation.

4.2. Exclusion Criteria

- Incomplete or retained products of conception will be excluded from the trial as there are no widely used criteria for deciding which women should have surgical evacuation.
- Suspicion of malignant gestational disease.

4.3. Co-enrolment

Co-enrolment of participants into other trials will be permitted unless the trial is specifically looking into the surgical management of miscarriage.

5. CONSENT

It will be the responsibility of the Investigator or delegate(s) to obtain written informed consent for each participant prior to performing any trial related procedure. Research nurses or midwives will be permitted to take consent providing local practice permits and this responsibility has been delegated by the Principal Investigator (PI) as captured on the Site Signature and Delegation Log).

A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators or delegate(s) will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given a minimum of 30 minutes to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before signing and dating the latest version on the Consent Form. If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

It is anticipated that some patients will be consented on the same day as the procedure because surgical management of miscarriage is sometimes done as an emergency, for example if the women is bleeding heavily. Also, logistically it might be easier to recruit women who are listed for surgical management of miscarriage on the day of the procedure to make sure there is a clinician able to carry out the surgery and someone who can perform ultrasound.

The Investigator or delegate(s) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU) trials team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients

approached about the trial that were not consented and randomised will be recorded on the Participant Screening/Enrolment Log and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Recruitment

Patients will be identified by doctors, research nurses and research midwives. All women undergoing a surgical evacuation of products of conception will be considered for the trial. Their clinical notes will be screened in order to ascertain eligibility. Only a member of the patient's existing clinical care team will have access to patient records in order to identify potential participants and check whether they meet the inclusion criteria or make the initial approach to patients.

All participants will be approached and recruited at a recruiting NHS hospital. A patient facing poster advertising the study will be displayed in clinically appropriate areas within the hospital.

Following a recent survey, 320 surgical evacuations are performed on average per year (60 evacuations under local anaesthetic and 260 under general anaesthetic). We will aim to recruit 90 participants in approximately 6 months.

6.2. Enrolment and Screening

The research team will work closely with the multidisciplinary team responsible for routine patient care. All women undergoing a surgical evacuation of products of conception will be considered for the trial. The trial will be introduced through a comprehensive, evidence-based patient information sheet that will be provided prior to the procedure. Participant information sheets and consent form will be provided to each centre in English and other languages in accordance with standard hospital procedures.

6.3. Randomisation

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at www.bctu-redcap.bham.ac.uk/SEEU). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the SEE U Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After participant eligibility has been confirmed by a research nurse or doctor and informed consent has been received, the participant can be randomised into the trial. Paper based randomisation notepads will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the

Randomisation Notepad must be answered before a Trial Number can be given. If data items are missing, randomisation will be halted, and the randomisation process restarted in the trial database once the information is available. Only when all eligibility criteria have been provided will a Trial Number be allocated.

Participants will be randomised at the level of the individual in a 1:1 ratio to either surgical evacuation of products of conception with intraoperative ultrasonography or surgical evacuation of products of conception without intraoperative ultrasonography.

Random permuted blocks of variable length will be used to ensure that the staff recruiting participants to the trial cannot reliably predict the next allocation. To ensure balance in the treatment allocation, randomisation will be stratified by the following variables:

- Proposed anaesthesia type (none/local or general);
- Randomising site

Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomising clinician, local PI, local Research Nurse and trial co-ordinating office.

Investigators will keep their own study file log, which links patients with their allocated trial number in the SEE U **Patient Recruitment and Identification Log**. The Investigator must maintain this document, which is **not** for submission to the Trials Office. The Investigator will also keep and maintain the SEE U Screening Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request. The SEE U **Patient Recruitment and Identification Log** and SEE U **Participant Screening/Enrolment Log** should be held in strict confidence.

6.4. Informing the participant's GP

If the participant has agreed, the participant's GP should be notified that they are in the SEE U trial, using the SEE U **GP Letter.**

6.5. Blinding

This will be an open trial design. It will not be possible to blind the surgeon from the use of ultrasound during the surgical management of miscarriage. If the procedure is performed under a general anaesthetic then the patient will be blinded from the intervention, but it will be obvious to the patient that ultrasound is being used if the surgical management of miscarriage is performed using local anaesthetic. Due to staffing restrictions it will not be possible to guarantee that the surgeon performing the hysteroscopy was not involved in the surgical management of miscarriage.

7. TRIAL TREATMENT / INTERVENTION

7.1. Surgical procedure

Surgical evacuation of the uterine cavity for the management of incomplete miscarriage generally involves vacuum aspiration or sharp metal curettage. Vacuum aspiration uses a soft or rigid suction catheter attached to a vacuum source for evacuation of the uterus. It can be used in the office setting without general anaesthesia and can be used with a hand-held vacuum syringe (Manual Vacuum Aspiration). This can be done with conscious sedation or with local anaesthetic. Sharp metal curettage is usually performed with regional or general anaesthesia in an operating room. Dilation of the cervix is not usually required in incomplete miscarriage and the metal curette is used to evacuate the contents of the uterine cavity. To maximise recruitment and generalisability the physician will be free to choose the exact method of surgical evacuation and the choice of anaesthetic, although the details of the treatment will be recorded. Serious complications of surgery can include: perforation of the uterus, cervical tears, intra-abdominal trauma, intrauterine adhesions and haemorrhage.

7.2. Intraoperative ultrasound

With intraoperative pelvic ultrasound the clinician is free to follow their usual procedure for evacuation of the contents of the uterine cavity. However, a second person performs a simultaneous abdominal pelvic ultrasound to allow visualisation of the cervix and uterine cavity.

Those performing the ultrasound and the surgeon need to be competent to use the ultrasound safely, as determined by their local hospital competency assessments. Training will be provided by the Chief Investigator on the correct use of ultrasound guidance for both surgeons and assistants in order to ensure the correct technique is used. Clear views of the uterine cavity and cervix are vital to ensure the safety of the procedure. When clear views are not possible due to increased bowel gas or patient adiposity it may be necessary to fill the urinary bladder with warm saline to ensure an acoustic window to improve visualisation of the uterus.

These scans are painless and safe. Unlike X-rays and other imaging tests, they do not use radiation. They have not been found to cause any problems or complications. Once the cavity appears empty on ultrasound the procedure is stopped.

7.3. Drug Interaction or Contraindications

All Rhesus negative women will be offered at least 250IU anti-D irrespective of their allocation. Prophylactic antibiotics will not be used. With the exception of the intraoperative pelvic ultrasound allocation following randomisation, all other aspects of patient management will be as the discretion of the local investigators.

7.4. Accountability Procedures

Surgical evacuation of the uterine cavity is widely performed across the NHS and is regarded as a safe procedure. Details of all procedures conducted will be recorded in the patient's

clinical notes, along with their subsequent outcomes. These data will be recorded in the case report forms.

7.5. Cessation of Treatment / Continuation after the Trial

A participant may be withdrawn from trial intervention if it becomes medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, SEE U study personnel will make every effort to obtain and record information about the reasons for discontinuation and any adverse events, and to follow up all safety and efficacy outcomes as appropriate.

8. OUTCOME MEASURES AND STUDY PROCEDURES

8.1. Clinical assessments and procedures

Procedural and baseline information will be collected prospectively during the intervention. Researchers will input the data directly onto a specifically created case report form. Baseline demographic information will include the patient's age, BMI, gestation, parity, if general anaesthesia is to be used, and type of miscarriage. The type of miscarriage included in this trial will be those diagnosed with early embryonic demise which is a delayed or missed miscarriage: The NICE guidance will be followed for the diagnosis of miscarriage (See box 1).

Following randomisation, the surgical procedure for the management of miscarriage will be conducted with or without intraoperative ultrasonography

Two to four weeks later, patients will be contacted to assess whether they have developed an infection after the procedure.

Four to eight weeks after the procedure, patients will undergo a follow-up hysteroscopy in the office setting without general anaesthesia. This is solely to identify if any intrauterine adhesions have formed following the surgical management of miscarriage. This is an important outcome because the prevalence of intrauterine adhesions is underestimated by clinicians and is thought to be related to the number of curette insertions and how vigorously the curettage in performed [18,19]. Two cohort studies reported 8-19% of women had intrauterine adhesions after surgical management of miscarriage [18,19]. Moreover, intrauterine adhesions can lead to menstrual disorders, infertility, pelvic pain and endometriosis.

Box 1. NICE guidance for diagnosis of non-viable intrauterine pregnancy

1.4.5
When performing an ultrasound scan to determine the viability of an intrauterine pregnancy, first look to identify a fetal heartbeat. If there is no visible heartbeat but there is a visible fetal pole, measure the crown–rump length. Only measure the mean gestational sac diameter if the fetal pole is not visible.
1.4.6
If the crown–rump length is less than 7.0 mm with a transvaginal ultrasound scan and there is no visible heartbeat, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.
1.4.7
If the crown–rump length is 7.0 mm or more with a transvaginal ultrasound scan and there is no visible heartbeat:
- seek a second opinion on the viability of the pregnancy and/or
- perform a second scan a minimum of 7 days after the first before making a diagnosis.

1.4.8
If there is no visible heartbeat when the crown–rump length is measured using a transabdominal ultrasound scan:
- record the size of the crown–rump length and
- perform a second scan a minimum of 14 days after the first before making a diagnosis.

1.4.9
If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.
1.4.10
If the mean gestational sac diameter is 25.0 mm or more using a transvaginal ultrasound scan and there is no visible fetal pole:
- seek a second opinion on the viability of the pregnancy and/or
- perform a second scan a minimum of 7 days after the first before making a diagnosis.

1.4.11
If there is no visible fetal pole and the mean gestational sac diameter is measured using a transabdominal ultrasound scan:
- record the size of the mean gestational sac diameter and
- perform a second scan a minimum of 14 days after the first before making a diagnosis.

1.4.12
Do not use gestational age from the last menstrual period alone to determine whether a fetal heartbeat should be visible.
1.4.13
Inform women that the date of their last menstrual period may not give an accurate representation of gestational age because of variability in the menstrual cycle.
1.4.14
Inform women what to expect while waiting for a repeat scan and that waiting for a repeat scan has no detrimental effects on the outcome of the pregnancy.

8.2. Process outcomes

To obtain estimates for important aspects of the protocol to allow development of a substantive trial, specifically:

1. To derive real-time data on the design aspects of the study:
    I. Proportion of eligible women of those screened: this will be the proportion of patients with miscarriage who are approached.
    II. Proportion of eligible women randomised: this will be the proportion of eligible patients randomised. A conversion rate of less than 33% will be considered unrepresentative and not sufficient to sustain a large study.
    III. Attrition rates: what is the follow-up rate at 2 to 4 and 4 to 8 weeks? We would expect follow-up rate to be at least 80%, using various methods of contact.
    IV. Proportion or women switching treatments: this will be the proportion of women randomised to a treatment that do not receive the assigned treatment.

2. To derive a realistic understanding of trial processes, in particular:
    IV. Ascertain robustness of the data collection process during and after the surgical procedure. We would expect completeness of important miscarriage treatment technique and early complication data to be over 90%.
    V. Determine the support required in units to ensure successful recruitment
    VI. Why patients decline participation or withdraw after randomisation. The reasons why women declined should be captured on the screening log. This could allow changes to the protocol to make participation within the trial more acceptable.

8.3. Evaluation of acceptability of processes and intervention for patients and staff

8.3.1. Acceptability and impact on patients

We will explore the acceptability of the intervention to patients and any impacts on their stay in hospital and post-discharge. All patients will be asked to provide feedback on their experiences of taking part in the trial, and how they feel it could have been improved. The patients will be asked for their feedback at their follow-up hysteroscopy appointment.

8.3.2. Acceptability and impact on clinical and research staff

Semi-structured qualitative interviews with clinical and research staff will be undertaken to explore the effectiveness and efficiency of the trial processes. This will include:

- The effectiveness of the patient identification and screening processes.
- Identification of reasons for failure to recruit patients.
- The willingness of gynaecologists to take part.
- The effectiveness of the randomisation process.

Interviews will also ask for staff ideas for improvement in trial processes, and explore whether there are any unintended consequences of the trial procedure, which might have an impact on patient care processes or the organisation and management of care.

Up to 20 staff interviews will be undertaken, which will be spread evenly across the three sites and will include the main clinical and managerial roles affected by the trial. The interviews will be undertaken in the month following the discharge of the last trial patient home. The interviews are expected to last an average of 20-30 minutes, and will be recorded digitally.

8.4. Clinical outcomes

8.4.1. Primary Outcome

The primary outcome will be composite consisting of any of the following: intrauterine adhesions (see section 8.4.5 for details); severe bleeding (defined as that requiring blood transfusion or total blood loss ≥500ml); infection and other post-operative complications (see section 8.4.5 for details); damage to the genital tract (cervical damage or uterine perforation); unsuccessful procedure (see section 8.4.6 for details).

8.4.2. Secondary Outcomes

- Rate of individual complications.
- Rate of serious adverse events.
- Need for additional surgical procedure(s) for miscarriage treatment.
- Need for medical management of miscarriage.

8.4.3. Procedure details

Components of the procedure considered as important include:

- The method of evacuation (manual vacuum aspiration, sharp curettage, suction curettage)
- When used, the size of the largest catheter used (measured in Hegar)
- The number of times a curette was passed into the uterine cavity
- Estimated blood loss (ml)
- Type of anaesthesia using for surgery
- Were uterotonic drugs used
- Was a balloon tamponade used
- Was antibiotic prophylaxis used
- Were products of conception observed

8.4.4. Intraoperative complications

Intraoperative complications are defined as any of the following:

- Anaphylaxis
- Bladder injury
- Uterine perforation
- Cervical damage
- Complications of anaesthesia
- Disseminated intravascular coagulation.
- Severe bleeding that requires a blood transfusion or total blood loss ≥500ml.
- Death
- 'Other' – we will collect complications that are not covered by the above list, which maybe included in the substantive study if they are thought to be relevant.

8.4.5. Post-operative complications

With the exception of intrauterine adhesions, these will need to have occurred within two weeks of treatment and are assessed 2-4 weeks following the procedure. Post-operative complications are defined as any of the following:

- Infection, with a definition based on CDC criteria and other studies as **two** or more of the following (without any **other** obvious cause of infection on history and examination): (1) uterine tenderness, (2) offensive vaginal discharge, (3) high temperature (4) white blood cell count > 12 x 10^9/L. To assess this, the patient will be contacted and asked whether they have suffered from: (1) pelvic pain beyond two days of the surgery, (2) offensive vaginal discharge, (3) fever or chills. If they report two or more of these patient-related symptoms then they will be invited in for clinical assessment in line with good clinical practice
- Haemorrhage requiring blood transfusion
- Disseminated intravascular coagulation
- Unplanned hospital admission due to a post-operative complication
- Intrauterine adhesions (defined as the formation of any filmy adhesions) identified at 4-8 weeks following the procedure with hysteroscopy. Pictures of the uterine cavity will be taken and passed on to hysteroscopists blinded to the randomisation. There will be up to five hysteroscopists who will make a majority decision on the presence of the intrauterine adhesions.
- Death

8.4.6. Unsuccessful procedure

Failed treatment is defined as any of the following:

- Failure to completely remove the products of conception during the initial evacuation.
- Positive pregnancy test three weeks after the procedure.
- Repeat surgical evacuation procedure(s) are required before telephone follow-up 2-4 weeks following the procedure.

- Medical management of miscarriage is required before telephone follow-up 2-4 weeks following the procedure.

8.5. Schedule of Assessments

Visit	Screening (Randomisation, surgery treatment forms)	Visit for surgery (Two week follow-up form)	2-4 weeks post-operative	4-8 weeks post-operative (Hysteroscopy treatment form)
Eligibility check	x			
Relevant medical history taken	x			
Concomitant medication	x	x	x	x
Valid informed consent		x		
Randomisation		x		
Surgical management of miscarriage		x		
Adverse events	x	x	x	x
Collection of outcome data		x		x
Telephone/ In person follow-up			x	
Follow-up office hysteroscopy				x
Site staff interview				x

8.6. Participant Withdrawal

A participant may be withdrawn from trial intervention if it becomes medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, SEE U study personnel will make every effort to obtain and record information about the reasons for discontinuation and any adverse events, and to follow up all safety and efficacy outcomes as appropriate.

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their on-going willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).
- The participant would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for post -

operative outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis.)

- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis).

or

- On rare occasion, the participant wishes to withdraw completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

9. ADVERSE EVENT REPORTING

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant this should be documented in the source data with reference to the protocol.

9.2. Adverse Events (AE)

There are certain AEs which are commonly expected in participants undergoing surgical management of miscarriage. As these events are well characterised, it is highly unlikely that this trial will reveal any new safety information relating to this intervention. The recording of selected AEs will therefore not affect the safety of participants or the aims of the trial.

AE that will be recorded in the Case Report Form (CRF) will include: uterine perforation, cervical trauma, bladder injury, complications of anaesthesia, anaphylaxis, disseminated intravascular coagulation, bleeding (as estimated blood loss in ml and those women requiring blood transfusion), repeat surgical evacuation, pelvic infection, repeat evacuation needed, unplanned hospital admission and intrauterine adhesions (Asherman's syndrome).

9.3. Serious Adverse Advents (SAE)

All events which meet the definition of serious will be collected and recorded in the participant notes and the Case Report Form (CRF). SAEs will in addition be reported to the trials office immediately and within 24 hours of being made aware of the event.

An SAE is an untoward event which:

- Results in death.
- Immediately threatens the life of the participant*.
- Results in hospitalisation or a longer than anticipated stay in hospital.
- Results in a persistent or significant disability.

**Life-threatening in the definition of a Serious Adverse Event or Serious Adverse Reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.*

9.4. Reporting period

The reporting period for AEs is up to 6 weeks post-surgery.

9.5. Reporting period – At Site

9.5.1. Adverse Events

Selected AEs should be recorded in accordance with the AE CRF. Records of AEs should be submitted via the trial electronic Remote Data Capture system (eRDC) as soon as possible.

9.5.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the PI will be asked to define the causality and the severity of the AE.

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

On becoming aware that a participant has experienced an SAE, the Investigator or delegates(s) should report SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the BCTU trials office, the Investigator or delegates(s) must complete, date and sign the trial specific BCTU SAE form. The completed form should be faxed or emailed to the BCTU trials team using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax or email the SAE Form to:

0121 415 9136

bwh-tr.tommysclinic@nhs.net

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via fax or email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within 1 working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.5.3. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a DCF, using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

9.6. Reporting Procedure – BCTU Trials Team

On receipt of a faxed SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the TMF.

On receipt of an SAE Form, the Chief Investigator (CI) or delegate(s) will independently determine the seriousness and causality of the SAE. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the CI or delegate(s) If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate(s) will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.7. Reporting to the Research Ethics Committee

9.7.1. Unexpected and Related Serious Adverse Events

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and RGT within 15 days.

9.7.2. Other safety issues identified during the course of the trial

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

9.8. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PI. A copy of any such correspondence should be filed in the site file and TMF.

9.9. Trial Oversight Committee

The independent TOC will review all individual SAEs and associated actions.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained. Source data is kept as part of the participants' medical notes generated and maintained at site.

10.2. Case Report Form (CRF) Completion

CRFs will be completed by research staff via the eRDC system. Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to CRF completion guidelines. This training will include:

- CRF completion and corrections
- Date format and partial dates
- Time format and unknown times

- Rounding conventions
- Trial-specific interpretation of data fields
- Entry requirements for concomitant medications (generic or brand names)
- Which forms to complete and when
- What to do in certain scenarios, for example when a subject withdraws from the trial
- Missing/incomplete data
- Completing SAE forms and reporting SAEs
- Repeat laboratory tests
- Protocol and GCP non-compliances

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator or delegate(s) on the CRF.

10.3. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial manager, statistician and programmer and the trial database will be signed off once the implementation of these has been assured. Trial data will be inputted directly into the database by the site from source data. All missing and ambiguous data will be queried by BCTU using data clarification forms (DCFs), which will be conducted on a monthly basis. Sites will be expected to resolve these queries within 4 weeks, and will be responsible for amending any incorrect data in the database. Any self-evident corrections will be identified and documented on a self-evident corrections form. Permission will be sought from the site's Principal Investigator before any of these self-evident changes are made to the trial data by a BCTU staff member.

10.4. Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the General Data Protection Regulation (GDPR) 2018. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.5. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. The centrally stored trial Master File will be archived in line with BCTU SOPs.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. In addition all local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Investigators and their host institutions will be required to permit trial-related monitoring and audits by the SEE U Trial Manager or a member of the trial monitoring team providing direct access to source data and documents as requested.

Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the SEE U trial staff access to source documents as requested. NHS Trusts may also be subject to inspection by internal Research and Development Managers, and should do everything requested by the CI in order to prepare and contribute to any inspection or audit. Study participants will be made aware by the PIS of the possibility of external audits of the data they provide.

11.3. Onsite Monitoring

Monitoring is carried out as required following trial specific risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the SEE-U trial staff access to source documents as requested. The monitoring will be conducted by the SEE-U trial management team.

11.4. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the monitoring plan.

11.5. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.6. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

12. END OF TRIAL DEFINITION

The end of trial will be four weeks after the last verified data capture. The BCTU trial team will notify the main REC and RGT that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report is also sent to the University of Birmingham RGT at the time of sending these are sent to the REC.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

The estimated sample size for the substantive study will be partially informed by the output from this pilot study but will be sufficiently powered to detect a minimally important reduction in rates of the composite measure. This study will aim to enroll 90 women. This number will allow us to measure the recruitment rate with 95% confidence interval (CI) width of approximately 10% if we assume 270 will be eligible over six months recruitment and we recruit a third of these.

13.2. Statistical Analysis

The study size is too small to allow reliable analysis of the effect of the intraoperative ultrasound on outcomes. Analyses of feasibility and clinical outcomes will primarily take the form of simple descriptive statistics (e.g. proportions & interquartile ranges, means and standard deviations) and where appropriate, point estimates of effects sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals. In the first instance, for clinical outcomes, participants will be kept in the groups they were allocated, regardless of compliance with treatment (intention-to-treat). A Statistical Analysis Plan will be generated for review by the Trial Oversight Committee before any analysis takes place.

13.3. Missing Data and Sensitivity Analyses

There is a potential for some missing data to occur at follow-up. However, in this context, this is part of the assessment of the success of the study and imputation of missing responses is not proposed.

13.4. Planned Interim Analysis

The Oversight Committee will meet prior to study commencement to agree the manner and timing of any analyses but this is likely to be limited due to the scope and timescales of the study recruitment period. If appropriate, criteria for stopping or modifying the study will be ratified by the Oversight Committee. Details of the agreed plan will be written into the Statistical Analysis Plan and the TOC charter. Further details of TOC arrangements are given in section 14.4.

13.5. Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the hysteroscopy assessment (at 4-8 weeks post-procedure) and corresponding outcome data has been entered onto the study database and validated as being ready for analysis.

14. TRIAL ORGANISATIONAL STRUCTURE

14.1. Sponsor

The sponsor for this trial is the University of Birmingham.

14.2. Coordinating Centre

The trial coordinating centre is Birmingham Clinical Trials Unit, based at the University of Birmingham.

14.3. Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial, and will include the CI, statistician and trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.4. Independent Trial Oversight Committee

The TOC will provide independent supervision for the trial, providing advice to the CI and co-investigators and the trial Sponsor, and affording protection for participants by ensuring the study is conducted in accordance with Good Clinical Practice (GCP) guidelines.

If the CI and co-investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TOC, drawing attention to any concerns they may have about the possibilities of particular side-effects, or particular categories of participants requiring special study, or about any other matters thought relevant.

14.5. Finance

The research costs of the trial are funded by a National Institute for Health Research (NIHR) post-doctoral research fellow grant awarded to Paul Smith and the University of Birmingham, reference PDF-2015-08-099. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs service support costs associated with the trial, e.g. gaining consent, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

15. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the General Data Protection Regulation, 2018) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation, 2018.

Participants will always be identified using their unique trial identification number and initials on the Case Report Form and any correspondence between members of the BCTU and trial team. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. sponsor). Representatives of the SEE U trial team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. Financial and other competing interests

There are no financial or other competing interests associated with this trial protocol.

18. Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. Amendments

The decision to amend the protocol and associated trial documentation will be initiated by the TMG. As sponsor, The University of Birmingham will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to REC and HRA for approval. Once this has been received, R&D departments will be notified of the amendment, and requested to provide their approval. If no response is received within 35 days, an assumption will be made that the site has no objection to the amendment and it will be implemented at the site.

All amendments will be tracked in the 'Protocol Amendments' section of the protocol.

20. Post-trial care

All patients will continue to receive standard medical care following the surgical procedure. Since this is a pilot study, there is no intention for the surgical evacuation of products of conception with intraoperative ultrasonography to be offered after the trial is completed. It is hoped that completion of this study will lead to a substantive study.

21. Access to the final trial dataset

Only the trial steering group will have access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication.

22. Publication Policy

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

23. Reference List

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