Sheffield Teaching Hospitals NHS
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The University Of Sheffield. Clinical Trials Research Unit.

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HELP Fertility?

Hysteroscopic Excision of Leiomyoma and Polyp
Does it improve fertility?

Other organisation Logos to be added

Hysteroscopic Excision of Leiomyoma and Polyp in Infertility: Two randomised controlled trials

RESEARCH PROTOCOL
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Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield Clinical Trials Research Unit (CTRU)

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Hysteroscopic Excision of Leiomyoma and Polyp in Infertility: Two randomised controlled trials

This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations

Definition of terms

AE	Adverse Event
ART	Assisted Reproductive Techniques
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
ESHRE	European Society of Human Reproduction and Embryology
GCP	Good Clinical Practice
HFEA	Human Fertilisation and Embryology Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICSI	Intracytoplasmic Sperm Injection
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
IUI	Intrauterine Insemination
IVF	In Vitro Fertilisation
LPLV	Last Patient Last Visit
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1. General information

1.1 Investigator details

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments

Version	Date	Summary of amendments
1.0	01.12.2020	N/A
2.0	26.04.2021	**Points of clarification:** • Details of REC, REC reference and ISRCTN registration added • correction to fibroid classification (type 0, 1, 2) **Eligibility screening:** Simplification of eligibility screening to a more pragmatic approach (2D ultra sound, as used by many sites, may be used to diagnose and measure fibroids and polyps in the assessment of eligibility). **Inclusion/exclusion criteria:**

		• modification of inclusion criteria 2 to include multiple fibroids and polyps amassing to 3cm or less in total. • removal of inverse inclusion criteria from list of exclusions (modification to exclusion criteria 1 and removal of exclusion criteria 2). **Data collection:** • Data collection window +2 weeks added for follow-up data collection time points. • Patient satisfaction questionnaire moved from 6-months post-hysteroscopy to +2weeks post-hysteroscopy. • Removal of hysteroscopy detail and patient cost data collection from control participants who withdraw from allocated treatment (decide to undergo hysteroscopy). **Adverse events:** • Expected Adverse event 'placenta accreta' expanded to include platenta, increta and percreta • Placenta abruption added as an expected adverse event • Removal of 'pain post procedure' as a specific procedure related expected adverse event – this will be a symptom of other expected events listed e.g. injury, bleeding, haemorrhage, infection etc.
3.0	12.07.2021	**Co-applicant details change for Mr Stuart Lavery** **Secondary Outcomes:** • Addition of COVID-19 vaccination status (1st, 2nd, booster, approximate date and type of vaccine) • Update of Table 2 to reflect data fields that will be collected, as per section 8.1. **Statistics – subgroup analyses** Amended to explain that a sub-group analysis, looking at interaction between treatment group and fibroid type, may be carried out if said data is available for a sufficient number of control patients.
4.0	Not issued	**Not issued**
5.0	11.11.2021 (CURRENT)	The trial is now registered on the NIHR Associate PI scheme Reference to Associate PI/Doctors added throughout. **<u>1.1 Administrative changes</u>** **<u>2.1 Background and rationale</u>**

		Removal of references to studies related specifically to unexplained fertility in section 2.1 to remove any ambiguity in relation to the study population. **<u>3.2 Objectives</u>** Removal of reference to unexplained fertility in the main trial objectives to ensure the objectives reflect the inclusion criteria. **4 Trial Design** Updated time frames due to potential impact of COVID-19 on the planned 2.5 year recruitment window. Removal of Gantt chart. **5.1 Inclusion criteria** Replacement of 'women of reproductive age' with 'women seeking fertility treatment', as the former infers age restrictions for recruitment. Addition of statement to clarify that women with known and unknown causes of infertility can be recruited, as intended. **5.3 Patient identification pathways** Note added to clarify identification of patients in initial phase ART and ovulation induction. **6.1 Patients randomised to intervention group** Paragraph added under heading 'Misdiagnosis' outlining course of action that should be taken. **<u>7.0 Randomisation and enrolment</u>** Addition of back-up randomisation plan in the event SCRAM is unavailable. **11.1 Sample size and 11.2 Statistical analysis** Addition of clinical pregnancy outcome as a proxy or surrogate outcome for the primary outcome (live birth rate) in the interim analysis, in order to inform a decision to alter the sample size of one or both of the trials.

Trial Summary

Study title	HELP Fertility?
Sponsor	Sheffield Teaching Hospitals NHSFT
Funder	National Institute of Health Research, Health Technology Assessment (NIHR, HTA)
ISRCTN	91356224
Project start date	April 2020
Project end date	October 2028
Hypothesis, aims and objectives	What is the clinical and cost-effectiveness of hysteroscopic removal of submucosal fibroids and endometrial polyps compared to no hysteroscopic removal, in women presenting with infertility and recurrent miscarriage? A) Assess the feasibility of conducting two multi-centre RCTs of hysteroscopic resection of endometrial polyps and submucous fibroids in women suffering from infertility or recurrent miscarriage, by conducting two RCT internal pilots; one for women with endometrial polyps and one for women with submucous fibroids; B) If feasible, determine the clinical and cost-effectiveness of the hysteroscopic removal of endometrial polyps and submucosal fibroids to improve fertility in women suffering from infertility or recurrent miscarriage; C) To determine patient experience and satisfaction, procedure related complications; D) To assess the long-term effect of hysteroscopic resection of endometrial polyps

	and submucous fibroids, by collecting and analysing routinely collected NHS data.
Trial design	An “Umbrella” RCT with two concurrent pragmatic, open, multi centre RCTs. Both trials involve 1:1 randomisation, hysteroscopic resection vs no hysteroscopic resection
Internal pilot criteria	Targets at 9 months; 30 centres set-up and recruited first participant Fibroid RCT: Average of 0.67 participants recruited per centre per month (approx. 117 participants recruited in total) Polyp RCT: Average of 1.3 participants recruited per centre per month (approx. 227 recruited in total) Withdrawal from control treatment: 0% of control participants received intervention before 6 months post randomisation Intervention waiting times: 100% of participants randomised to the intervention (resection of fibroids or polyps) receiving the treatment before 3 months post-randomisation. Detailed green/amber/red criteria for both RCTs are included in section 8.1
Setting	Secondary and tertiary fertility or gynaecology units providing care for women with infertility and recurrent miscarriage

Participants	Inclusion criteria; 1) History of primary or secondary infertility or recurrent miscarriage, as defined in section 5.1 2) Diagnosed endometrial polyps or submucosal fibroids 3 cm or less in size (or amass to 3cm or less in total) Exclusion criteria; 1) The presence of additional medical morbidity as a result of the submucous fibroid or endometrial polyp such as anaemia due to heavy periods or significant pain which necessitates surgical intervention 2) Asherman's syndrome 3) Malignancy of endometrial polyp/submucous fibroid is suspected 4) The patient is taking part in any other interventional infertility trial 5) Pregnancy, or pregnancy is suspected. 6) Previously randomised into the other trial (RCT 1 and RCT2)
Intervention & control groups	Intervention group: hysteroscopic removal of submucous fibroids and / or endometrial polyps. Control group: no hysteroscopic removal of submucous fibroids and / or endometrial polyps.
Primary outcome(s)	Live birth rate (LBR) at 15 months post-randomisation
Secondary outcome(s)	- LBR at 24 months post-randomisation - Time from randomisation to live birth - Time from randomisation to pregnancy

	- Clinical pregnancy, miscarriage, premature labour, multiple birth, still birth and ectopic pregnancy rates - Detail of hysteroscopy received - Patient satisfaction - Details of fertility treatments received, including details of medications received and assisted reproductive techniques received - Incorrect diagnosis/absence of abnormalities at surgery - Type of submucous fibroid (type 0, 1, or 2). - Number of participants randomised to the control arm (no resection of fibroids or polyps) who receive the treatment (resection) before 6 months post-randomisation. - Number of participants randomised to the intervention (resection of fibroids or polyps) who receive the treatment before 3 months post-randomisation. - Adverse events (procedure related and gynaecological/obstetric related complications) (refer to section 10) - Health resource use and patient cost - Cost per live birth gained Long term outcomes (minimum 5 years post randomisation): - Live birth rate - miscarriages, terminations and still births - details of fertility treatments - details of hysteroscopy received
Duration of recruitment period and first enrolment date	Duration of recruitment period: 2 years and 6 months (pre-COVID-19 pandemic plan)

	First enrolment date for the pilot phase will be July 2021
Duration of follow-up	Minimum of 24 months post-randomisation (participants to be followed up to the last participant completing the 24-month data collection) Long-term follow up at least 5 years post randomisation
Target sample size	1120
Definition of end of trial	Completion of the 24-month follow-up by the last participant recruited (last patient last visit, LPLV)

2. Introduction

2.1 Background and rationale

Uterine fibroids remain the commonest benign tumours of the female genital tract affecting 20-40% of women in the reproductive years and are commonly encountered in women undergoing fertility treatment (1). Intracavitary fibroids have been reported in around 5-18% of patients with infertility and about 7% of women with unexplained infertility (2,3). There is evidence, largely from observational studies, that submucous fibroids may have a negative effect on reproductive performance (4) by both distorting the endometrial cavity and possibly disrupting subendometrial blood flow (5). Surgical removal of these fibroids in order to improve reproductive performance has become widely accepted practice (6), despite the existing evidence to support the resection of fibroids coming largely from small observational studies with a clear lack of good quality randomised controlled trials (6,7).

Endometrial polyps are also a common finding, occurring in an estimated 11-45% of women undergoing in vitro fertilisation and 15-25% of women with unexplained infertility (2,8,9). Endometrial polyps may have a negative effect on fertility as evidenced by a negative effect on markers of endometrial receptivity such as HOXA10 and HOXA11 mRNA levels (8). Based on the assumption that these polyps can adversely affect reproductive performance, hysteroscopic removal, similar to submucous fibroids, has become a popular intervention in women with fertility problems despite the fact that this practice is not yet supported by a body of evidence from randomised controlled trials (10). Most of the studies that have examined the effect of endometrial polyps on pregnancy rates were small observation non-controlled studies (10–19) and, amongst these studies, there is controversy regarding whether or not they have a negative effect on conception rates. This suboptimal quality and conflicting nature of the evidence was highlighted in a 2010 systematic review (20). The most recent meta-analysis has shown an increase in clinical pregnancy rates after hysteroscopic resection of fibroids after intrauterine insemination but not after In Vitro Fertilisation (IVF) and has highlighted the importance of more randomised controlled trials (21).

Hysteroscopic removal of polyps and fibroids is not without risks, some of which, such as uterine perforation, Asherman's Syndrome and intrauterine adhesions, may have a negative effect on fertility (22,23). Surgery poses a significant economic burden on an already burdened National Health Service (NHS), and can cause the patient significant anxiety, affecting pain perception and satisfaction (24).

Due to the poor quality of the existing evidence and as highlighted by the National Institute for Health and Care Excellence (NICE), Health Technology Assessment (HTA) brief and the Cochrane review (6,25), further research is needed to determine whether hysteroscopic removal of these uterine cavity abnormalities is beneficial; not only in increasing the live birth rates to help inform and guide practice but also in relation to the significant economic burden placed on the NHS by performing a procedure with inadequate evidence (1).

Currently hysteroscopic removal of submucous fibroids and endometrial polyps is being routinely performed in the NHS for women with infertility including those where no particular other impediment to fertility can be found (unexplained infertility) and women with recurrent miscarriage. This is despite NICE guidance stating that the effectiveness of surgical resection has not been established (25). The procedure poses a significant cost to the NHS. In addition, surgery carries risks, some of which may cause further detriment to fertility and costs to the NHS – these risks include uterine perforation, fluid intravasation and Asherman's syndrome (6,29).

If resection of fibroids and polyps does indeed improve reproductive performance, then this would have a potential influence on existing fertility pathways. For example, the NICE guidelines for fertility management suggest that IVF is the optimum treatment for women with unexplained infertility (25). Funding for IVF however is variable and inconsistent across the UK and is often limited to a single cycle. If women with submucous fibroids or polyps associated with unexplained infertility were to benefit from resection of these lesions, then in many cases IVF treatment could be avoided with consequent cost savings to both the NHS and to self-funding patients.–There is a current trend towards local authorities reducing funding for fertility treatments, thus increasing the burden on patients to fund this treatment themselves. Given this, and the emotional and medical side effects of receiving such treatments, it is imperative that evidence is created to guide clinicians and patients on the effects of hysteroscopic resection so that they can make an informed decision in relation to the patient's chances of live birth (30). There is therefore a current urgent need for a well-designed definitive study examining the effect of hysteroscopic resection of submucous fibroids and polyps in the two distinct populations of women with infertility and women with recurrent miscarriage, whether being managed expectantly or with active fertility interventions.

3. Aims and objectives

3.1 Aims

To examine the clinical and cost-effectiveness of hysteroscopic removal of submucosal fibroids and endometrial polyps compared to no hysteroscopic removal in women presenting with infertility and recurrent miscarriage.

3.2 Objectives

The main trial includes an internal pilot to determine the feasibility of site set-up and participant recruitment, the waiting times for the intervention group to receive resection and the number of control participants who undergo resection.

Internal pilot objectives:

A. To assess the feasibility of conducting two multi-centre RCTs of hysteroscopic resection of submucous fibroids and endometrial polyps in women suffering from infertility or recurrent miscarriage, by conducting two RCT internal pilots; one for women with endometrial polyps and one for women with submucous fibroids.

Main trial objectives:

The objectives of the main trial are:

A. To determine the clinical and cost-effectiveness of the hysteroscopic removal of endometrial polyps compared to no hysteroscopic removal to improve fertility in women suffering from infertility or recurrent miscarriage.
B. To determine the clinical and cost-effectiveness of the hysteroscopic removal of submucous fibroids compared to no hysteroscopic removal to improve fertility in women suffering from infertility or recurrent miscarriage.
C. To determine patient experience and satisfaction, and procedure related complications.
D. To assess the long-term effect of hysteroscopic resection of endometrial polyps and submucous fibroids, by collecting and analysing routinely collected NHS data.

The outcomes used to assess these objectives are described in section 8.

4. Trial Design

The following study will be conducted in accordance with the protocol and ICH GCP.

The trial is designed as an "Umbrella" RCT (31) with two concurrent pragmatic, parallel group, open, multi centre RCTs. Methods for each RCT will be the same except where described here separately. A trial summary flow diagram is provided in Figure 2.

RCT1: Submucous fibroid population: women with a history of infertility or recurrent miscarriage and trying to conceive naturally or with fertility treatment and who meet the inclusion criteria will be randomised (1:1) into hysteroscopic resection vs no hysteroscopic resection of the submucous fibroid.

RCT2: Endometrial polyp population: women with a history of infertility or recurrent miscarriage and trying to conceive naturally or with fertility treatment and who meet the inclusion criteria will be randomised (1:1) into hysteroscopic resection vs no hysteroscopic resection of the endometrial polyp.

Patients and clinicians will not be blinded to which arm of the study the participant is randomised to, due to the nature of the intervention. The primary outcome of live birth rate will be collected at 15 months post randomisation, with participants being followed-up at 6 months, 15 and a minimum of 24 months post-randomisation. The pre-COVID-19 plan for recruitment was 2.5 years. Women recruited to the trial will have at least 4.5 years follow-up in the main trial (randomisation to 24mth follow-up plus 2.5 years to last patient last visit, LPLV). Participants will be followed up for an additional 3 years in the long term study.

An economic evaluation will be undertaken to determine the cost-effectiveness of submucous fibroid and endometrial polyp resection.

Internal pilot

Each trial will commence with a 9-month internal pilot phase across approximately 30 sites to determine whether the recruitment strategy and site set-up are feasible, whether participants randomised to intervention receive resection within an acceptable timeframe (set at 3-months post randomisation) and whether the level of withdrawal from the control treatment (i.e.the numbers of women in the control arm who undergo resection) is acceptable. The pilot study will use the same trial procedures as later described for the main trial.

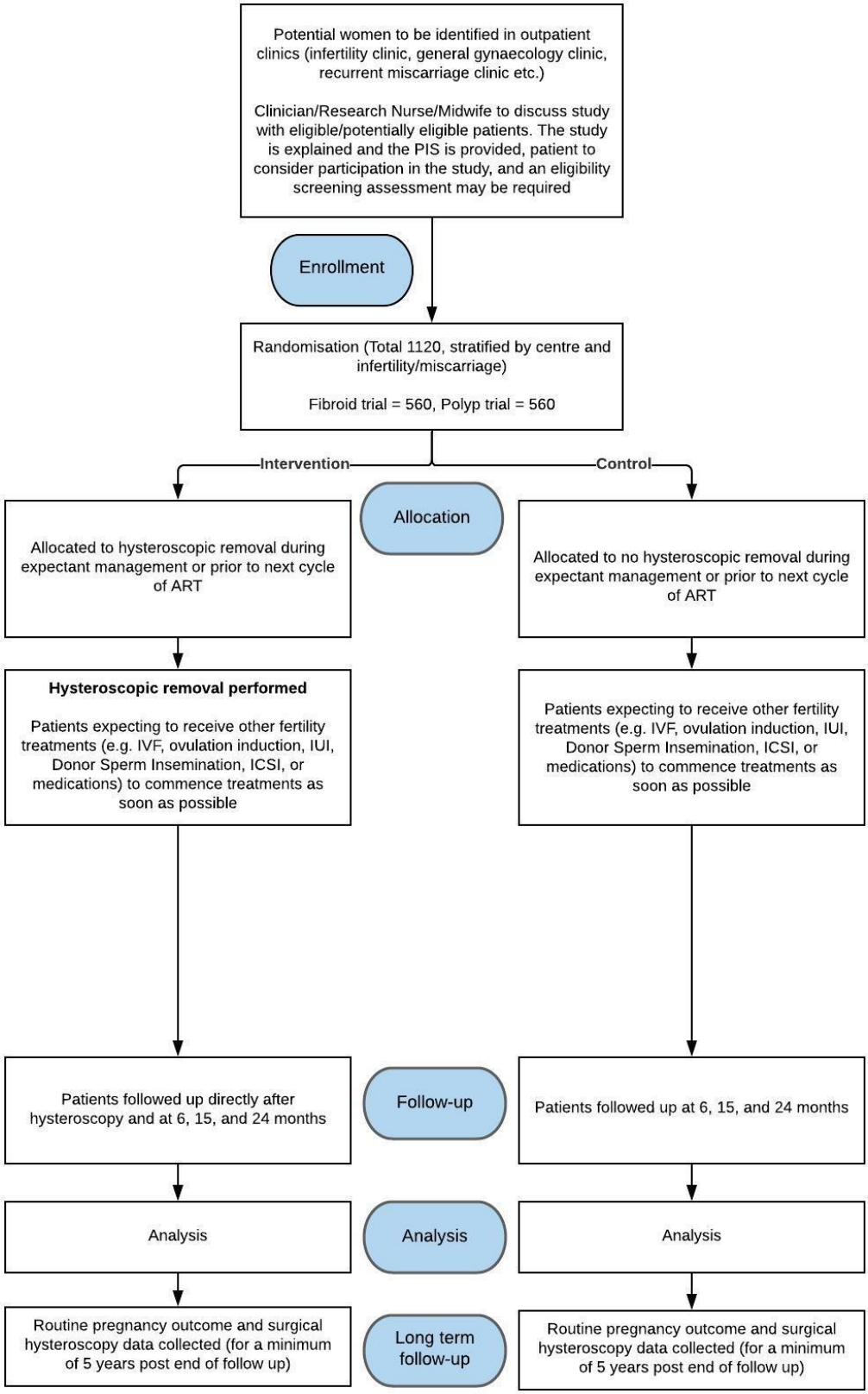
Main study

Following successful completion of the internal pilot, each trial (RCT1 and RCT2) will aim to recruit a total of 560 patients from approximately 30 centres across the UK, over 30 months (recruitment target includes participants recruited to the 9-month internal pilot). Eligible women will be randomised to receive either hysteroscopic resection of the abnormalities (intervention group) or no hysteroscopic resection (control group).

Long term follow-up study

A long term follow up study will be undertaken using data available in medical notes and / or routine NHS data – each participant will be followed up for a minimum of 5 years to collect pregnancy outcomes, fertility treatment and whether hysteroscopic resection of the abnormalities has been undertaken. Participants will be asked at recruitment if they are willing for the research team to access this data from hospital/clinic medical records and from NHS Digital; participants will indicate permission for this on the trial consent form.

Figure 2 Trial summary flow



5. Selection of participants

Trial Setting

Approximately 30 centres across the UK including secondary and tertiary fertility or gynaecology units providing care for women with infertility and recurrent miscarriage. The treatments these units provide may include expectant management, ovulation induction, in vitro fertilisation (IVF), intrauterine insemination (IUI), Donor Sperm Insemination, or intracytoplasmic sperm injection (ICSI). Smaller district/local hospitals that treat patients early on in their fertility journey prior to receiving assisted reproductive technology (ART) will also be included.

Trial population

This study aims to recruit women with infertility or recurrent miscarriage who have a confirmed diagnosis of endometrial polyps or submucous fibroids. Women will be identified from gynaecology, recurrent miscarriage, infertility clinics as well as assisted conception units. Women with both an endometrial polyp and submucosal fibroid will be recruited and randomised into the trial for whichever abnormality is larger in size. Women with previously resected endometrial polyps or submucous fibroids, who have developed a further abnormality, will be potentially eligible for participation in these trials (except those who have already been randomised into one of the trials, RCT1 or RCT2).

5.1 Inclusion criteria

The following criteria will be used to decide if potential participants are eligible for the trial:

1) History of primary or secondary infertility (defined as a woman seeking fertility treatment who has not conceived after 1 year of unprotected sexual intercourse, in the absence of any known cause of infertility, or earlier if there is a known cause

   OR

   A woman seeking fertility treatment who is using artificial insemination to conceive (with either partner or donor sperm) if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility, or less if there is a known cause

   OR

   History of recurrent miscarriage (defined as the loss of two or more pregnancies before 24 weeks gestation).

2) Diagnosed endometrial polyps or submucosal fibroids that are 3cm or less in size OR in cases where multiple fibroids and or polyps are present, these amass to 3cm or less in total (diagnosis

and measurements obtained using the assessment methods, or combination of assessment methods described under section 5.3.1).

5.2 Exclusion criteria

The following exclusion criteria will be applied:

1) The presence of additional medical morbidity as a result of the submucous fibroid or endometrial polyp, such as anaemia due to heavy periods or significant pain which necessitates surgical intervention.

2) Asherman's syndrome

3) Malignancy of endometrial polyp/submucous fibroid is suspected.

4) The patient is taking part in any other interventional infertility/fertility trial

5) Pregnancy, or pregnancy is suspected.

6) Previously randomised into the other HELP Fertility? trial (RCT 1 or RCT2)

5.3 Participant identification pathways

Women for both trials will be identified either as incidence cases, as they attend a fertility or recurrent miscarriage clinic and the presence of polyps or fibroids are confirmed, or via review of medical notes to identify those women who have had polyps or fibroids diagnosed but not resected. Women will be identified at any point during their fertility journey as detailed in pathways 1 and 2 below.

NOTE: Patients can be approached in the initial phase of an ART cycle prior to egg collection, embryo transfer, during initial ovarian stimulation or ovulation induction if a polyp or fibroid is unexpectedly identified. The ART cycle may be paused until the management of the patient is clarified, as per usual standard of care. For patients who participate in the trial this may mean pausing until randomisation has taken place.

Sites should confirm the woman is not pregnant.

Pathway 1 – Eligible participants (see Figure 3)

Women who are identified during a clinic appointment, from medical notes or a database search as **eligible,** i.e. have a diagnosis and accurate measurement of fibroids and or polyps which are recorded in the medical notes, should be provided with the patient information sheet (PIS) ***(document: PIS)***. In some cases, where the woman is identified via medical notes/database

search and an accurate measurement of size has not been recorded in the notes, a scan may be required to confirm eligibility (see section 5.3.1).

Pathway 2 – Sites that routinely diagnose fibroids and polyps by hysteroscopy AND have capacity and agree to perform randomisation during hysteroscopy (a technique that has been utilised in previous randomised trials (32)**, see Figure 4)**

In these cases, the trial will be explained to the patient before undergoing hysteroscopy and informed consent taken prior to any study related procedures being performed ***(document: ICF)***. For the purpose of confirming eligibility for the trial, one other imaging technique will be used either before or during the hysteroscopy, to provide a measurement of the fibroids and/or polyps (examples given in section 5.3.1). If it is confirmed that the patient meets the eligibility criteria, the patient will be randomised during hysteroscopy. If randomised to the intervention arm, the endometrial polyp/submucous fibroid will be resected. If randomised to the control arm, the endometrial polyp/submucous fibroid will **not** be resected and the procedure will cease.

The assessment of eligibility will be undertaken by the principal investigator or another suitably qualified member of the research team, who has received appropriate training and has been approved by the principal investigator as detailed on the delegation of responsibilities log.

5.3.1 Eligibility assessment methods

It is recognised that imaging and screening capability at sites may vary. Eligibility assessment for this trial is designed to be inclusive of all methods that may be used routinely. All patients taking part in the trial MUST have undergone assessment(s) to confirm eligibility, using the sites usual procedures to A) diagnose fibroids and/or polyps and B) confirm measurement of 3cm or less in size (multiple fibroids and / or polyps should amass 3cm or less). Example methods: 2D or 3D ultrasound scan, CT/MRI scan, hysterosalpingography, Hysterosalpingo Contrast Sonography (HyCoSy), Saline Sonography, hysteroscopy.

NOTE: Sites routinely performing diagnostic hyeteroscopy or Saline Sonography should use one other imaging technique, capable of accurate measurement of the fibroids and / or polyps e.g. 2D or 3D ultrasound scan, CT/MRI scan.

Figure 3 - Participant pathway 1 from eligibility assessment to treatment allocation

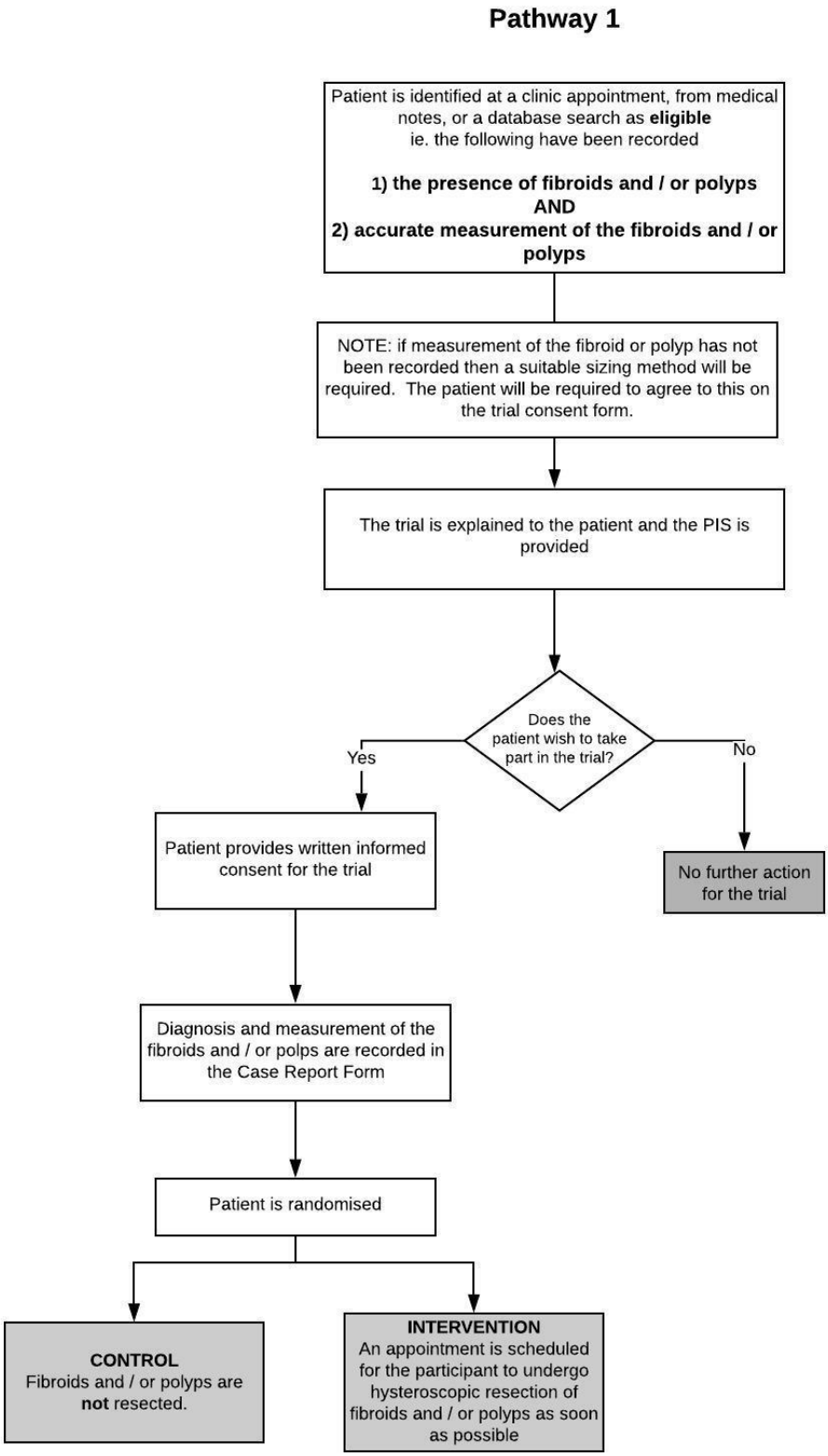
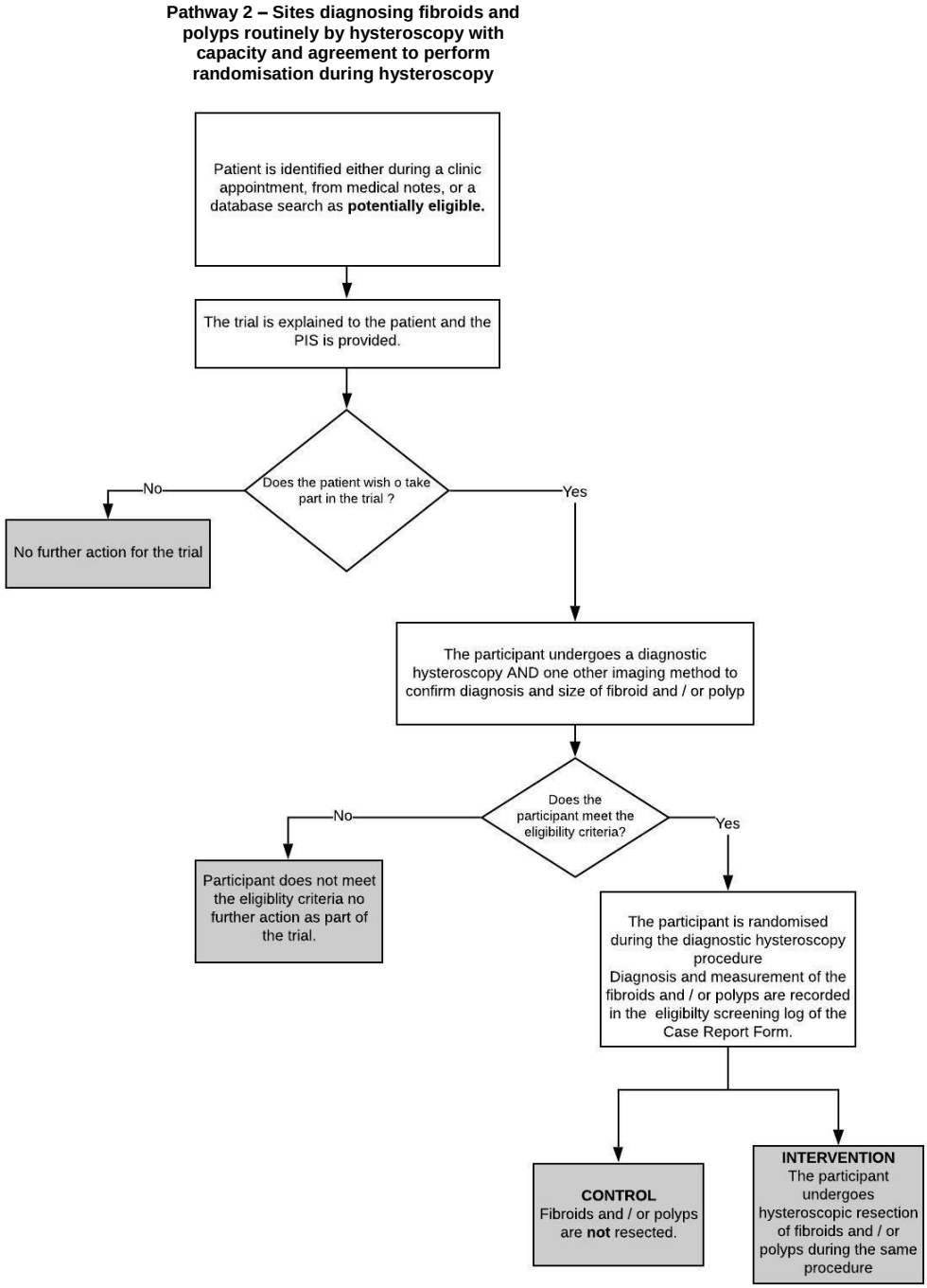


Figure 4 - Pathway 2 Sites with capacity and agreement to perform randomisation during hysteroscopy



5.4 Informed consent

Resection of submucous fibroids and endometrial polyps is such common practice that site staff and patients may perceive allocation to the control group as a lack of intervention and a detriment to their fertility treatment. Study specific training for staff will be designed to deliver a balanced view of the trial (see section 17.1). A recruitment video, consisting of information from the PIS, will be made available to participants via online platforms (e.g. YouTube) to view at any time prior to or during the consent procedure.

5.4.1 Informed consent process

The assessment of eligibility and the process of informed consent will be undertaken by the principal investigator or another suitably qualified member of the research team, who has received appropriate training and has been approved by the principal investigator as detailed on the delegation of responsibilities log. All staff involved in taking informed consent for the study will have a thorough knowledge and experience of GCP and issues around informed consent, and be fully trained in the study protocol.

1. Potentially eligible women will be informed about the study via one of the following routes:

    a) Women may be told about the study and receive the PIS at a clinic appointment ***(document: PIS)***

    b) Women may receive a letter of invitation introducing the study (in the post, or by email) and a copy of the PIS will be included ***(documents: PIS, Invitation Letter, Invitation Email)***.

    c) Women may be informed about the trial via the website, recruitment video (based on the PIS) or a poster and will be advised to discuss the study with their Clinician/Research Nurse/Midwife/AssociatePI/Dr documented on the trial delegation log ***(document: Recruitment Poster)***

Potential participants may be approached at any point in their fertility journey (as per section 5.3) via a letter or email or by a member of their research/fertility team ***(documents: Invitation Letter, Invitation Email)***.

Regardless of which method is used to approach women, they may be contacted by a member of the research team (Dr/Nurse/Midwife) via post, email, telephone or text message to ask if they are interested in participating in the study ***(documents: Recruitment Follow-up Letter, Recruitment Follow-up Email, Recruitment Follow-up text)***. Further contacts will be attempted

up to approximately two weeks after the woman has first been alerted to the study via any of the methods outlined above. The clinical research team member (clinician, research nurse/midwife/Associate PI/Dr or another with relevant experience and training and recorded on the delegation log) will ask the potential participant if she has any questions related to involvement in the study and will either a) confirm with the participant the date/time of their next routine visit, and confirm that consent will be sought on that day either in person, online or by post ***(document: ICF)***, or b) if the woman is not interested in participating in the study, will confirm that the participant will not be contacted again.

2. Eligible women will be invited to participate and will be given as much time as required, to ask questions about the study and discuss their participation with their clinician/research nurse/midwife/clinic nurse/Associate PI/Dr.

3. Following consent, the participant's details will be recorded on the trial enrolment log.
Baseline data including health & wellbeing questionnaires must be collected prior to or at the point of randomisation. If consent is refused or if the patient is not eligible then the reasons for refusal/ineligibility will be requested, basic information will be recorded to enable completion of CONSORT diagram.

4. A record of the consent process detailing the date of consent and all those present will be recorded in the participants' hospital notes. The original consent will be filed in the investigator site file, a copy retained in the hospital notes and a second copy will be given to the participants. Where e-consent is provided the CTRU will send a copy to the recruiting site for filing in the site file and medical notes and a copy will be sent to the patient electronically. With the participants' consent, their GPs will be notified using the REC approved GP letter provided ***(document: GP Letter)***.

If any further safety information which may result in significant changes to the risk/benefit analysis is identified, the PIS and informed consent form (ICF) will be reviewed and approved accordingly. All participants who are yet to receive the intervention will be informed of the updated information and given a revised copy of the ICF to sign, confirming their wish to continue in the study.

5.4.2 Consent methods

The methods for providing consent are outlined below;

1. Written consent at a clinic appointment

Potential participants wishing to take part can provide written informed consent at a clinic appointment with a trained member of the clinical research team ***(document: ICF)***. Informed consent can be taken either at the time of the initial medical or nurse consultation at the participating clinic/hospital or at a later time during a routine fertility appointment, for example women who have been given information about the study at an earlier date and have expressed their interest to participate. Participants will be given a copy of the Informed consent form to keep for their records.

2. Video/phone call and written consent via post

Potential participants may be sent the PIS in the post or via email ***(document: PIS)***, and will have the chance to discuss the study and ask questions with a trained member of the clinical research team during a pre-arranged phone or video call (sites may use any video conferencing software that is approved for use at their hospital). A blank copy of the consent form will be posted to the participant with a prepaid return envelope for them to initial, sign, date and send back ***(document: ICF)***. Baseline measures cannot be undertaken until the signed consent form is received. Participants will be posted/emailed a signed copy of the consent form to keep for their records.

3. Video/phone call and e-consent form using the online system

Potential participants may be sent the PIS in the post or via email ***(document: PIS)***, and will have the chance to discuss the study and ask questions with a member of the clinical research team during a pre-arranged phone or video call (sites may use any video conferencing software that is approved for use at their hospital). The participant will be emailed a link to an online consent form. The potential participant will be asked to tick the boxes next to each consent statement and will not be able to proceed/complete the form until the relevant boxes are ticked. A PDF of the completed Informed consent form will be created and sent to the participant to keep for their records and 2 further copies will be filed in the site file and medical notes as described above.

The doctor or nurse will emphasise that participation is entirely voluntary and that choosing not to participate will not negatively influence the woman's treatment in any way. The right of the patient to refuse consent without giving reasons will be respected. Furthermore, the participant will remain free to withdraw from the study at any time without prejudicing any further treatment.

It is not foreseen that participants will be lacking in physical or mental capacity to provide informed consent. Where the patient has the capacity to provide informed consent but is unable to sign or otherwise mark the consent form, we will follow the same procedure which the clinic adopts for

such cases in regards to signing HFEA (Human Fertilisation and Embryology Authority) consent forms for assisted conception treatment, as specified by the HFEA:

> "If the person giving consent, or varying or withdrawing consent, has the mental capacity to do so but cannot sign because of illness, injury or physical disability (for example, quadriplegia), they can direct someone to sign on their behalf, provided that:
> a) the person giving consent, or varying or withdrawing consent is present at the time, and
> b) the signature is also witnessed, and attested to by at least one other person."

If a translator is needed, the study team will endeavour to make available the provision of a translator service in the spoken language of the participant per standard local NHS Trust arrangement.

6. Trial treatment

6.1 Patients randomised to Intervention Group

Hysteroscopic resection of submucous fibroids and endometrial polyps is currently undertaken routinely in the NHS for women suffering from miscarriage or infertility.

In order for this study to be applicable to the wider NHS, a pragmatic approach will be taken, and hence we will accommodate local hysteroscopic procedures conducted at the participating centres using existing surgical techniques and setups. Techniques will include the use of bipolar or monopolar resectoscopes, hysteroscopic morcellators or scissors or polyp snares. The procedure may be performed in an outpatient or inpatient setting. For large abnormalities, further surgical procedures may be required. Type 0 and Type I submucous fibroids are more easily resectable than Type II. Clinical / operator judgement will be used to determine the intra-cavitary portion that is resectable for Type II fibroids. As per usual practice, women randomised to receive the intervention will be asked to use contraception prior to hysteroscopy taking place, if applicable. A pregnancy test may also be undertaken. This is in line with routine clinical care and the World Health Organisation (WHO) checklist prior to resection (33). In the event that a patient allocated to intervention has a positive pregnancy test before receiving hysteroscopic resection, the patient will remain in the trial and followed-up as per the schedule in 9.1.

Scheduling treatment

For participants allocated to the intervention group, sites should aim to schedule the appointment for hysteroscopic resection within the 18-week patient pathway. However, with the current COVID-19 pandemic the procedure should be scheduled within the site's own current guidelines. Participants expecting to receive other fertility treatments e.g. IVF, ovulation induction, IUI, Donor Sperm Insemination, ICSI or medications e.g. clomid, should commence with this treatment as soon as possible following hysteroscopic resection. This does not include any research infertility interventions as these are exclusion criteria.

Compliance

Compliance to the randomly allocated treatments (intervention or control) will be ascertained through the clinician or Research Nurse/Midwife/Associate PI/Dr recording whether or not the patient has a) attended the clinic for the hysteroscopic excision of submucous fibroids and or endometrial polyps and b) received the procedure per protocol (following the sites usual procedures for hysteroscopic removal of submucous fibroids and / or endometrial polyps). Any deviation from the protocol will be noted and reported as per the CTRU SOP.

Intervention participants may wish to withdraw from receiving the intervention, or there may be a clinical need to withdraw the participant. Control participants may wish to undergo hysteroscopic resection. This does not mean the participant is withdrawing or being withdrawn from the trial. See section 9.2 and 9.3 for withdrawals.

Misdiagnosis

It is possible that fibroids and /or polyps identified at the patient screening / eligibility stage are found to have been misdiagnosed when carrying out hysteroscopic procedure. This will be confirmed by the histology result. For example, a uterine abnormality **diagnosed** as a fibroid may be a polyp and visa versa. In these cases, the misdiagnosis should be recorded in the patient medical notes and captured in the 'Hysteroscopy CRF' within the Prospect database. The patient will remain in the RCT (polyp or fibroid) to which they were randomised and the data will be analysed as part of the 'intention to treat' statistical analysis.

6.2 Patients randomised to Control Group

Participants randomised to the control group will not receive hysteroscopic resection of their submucous fibroids or endometrial polyps. Participants expecting to receive other fertility treatments e.g. IVF, ovulation induction, IUI, Donor Sperm Insemination, ICSI or medications e.g.

clomid, should resume/commence with this treatment as soon as possible following randomisation. This does not include any research infertility interventions as these are exclusion criteria (exclusion criteria 4).

Women with a strong preference for resection will not be recruited. However, women will have the right to withdraw from their randomised treatment at any time, as is their right (detailed in section 9.2).

7. Randomisation and enrolment

Eligible and consenting participants will be randomised using a centralised web-based randomisation system (SCRAM) hosted by Sheffield Clinical Trials Research Unit (CTRU). This system has user restricted functionalities depending on trial roles. Participants will be allocated on a ratio of 1:1 to either receive hysteroscopic resection of the abnormalities (intervention group) or not (control group). Stratified block randomisation will be used, stratified by 1) recruiting centre and 2) infertility or recurrent miscarriage (both defined in section 5.1). We will not disclose block sizes during the trial. A Trial Statistician will generate the allocation sequence using the SCRAM system. Research staff at recruiting centres will be unable to access the randomisation sequence. A member of the clinical research team will enter participant details onto the system prior to randomisation in order to maintain allocation concealment. Following randomisation, the participant will be informed of their allocation and a record of this will be entered into the patient's medical notes and the next steps in treatment arranged. Some sites may have capacity to facilitate randomisation during the hysteroscopic procedure. In these cases, women randomised to intervention will receive resection during the same procedure. Women randomised to control will not receive resection. Women who are randomised into one of the trials but then go on to develop an abnormality that would render them eligible for the other trial (e.g. randomised into the endometrial polyp trial but then goes on to develop a submucous fibroid) will not be re-randomised and will remain in the trial in which they were originally allocated to, as per ITT (Intention to Treat) principles.

If site staff are unable to access SCRAM, randomisation will be performed centrally by an unblind member of the CTRU team using the same SCRAM system. In the unlikely event SCRAM were to be unavailable, separate back-up randomisation lists will be used. Lists, stratified by site and trial, will be generated by a statistician independent of the HELP study and held in a restricted-access directory on a university drive. Site staff and blinded CTRU staff will not be able to access

the back-up randomisation schedule. Requests for central randomisation can be made via a study-specific email address / telephone number, which will be made available to the site.

7.1 Blinding

The Trial Steering Committee (TSC), the study statisticians and health economists will be blinded to treatment allocation whilst the trial is ongoing. Participants and site staff cannot be blinded due to the nature of the intervention.

7.2 Unblinding

Unblinding of trial statisticians, health economists and the TSC will not take place until the statistical and health economics analysis plans are approved and final data entry and cleaning has taken place (after the final 24 month data collection and again 5 years after consent of the last participant, for the long term follow-up data).

8. Outcomes

8.1 Feasibility outcomes

We have followed the recommendations of Avery et al in setting green/amber/red criteria for both RCTs (34), where green indicates continuation of the trial, any amber indicates that steps should be in place to regain ground and any red indicates the trial is not feasible. Targets will be assessed following 9 months of a 30 month recruitment window. Recruitment targets factor in a staggered site set-up over 7 months. Participant retention will not be assessed as the primary outcome data collection point occurs at 15 months post-randomisation and so inclusion within the stop/go assessment timeframe is not possible.

It is anticipated that the COVID-19 pandemic will impact site waiting times for hysteroscopic resection and these will be monitored during the pilot phase. Timing of primary outcome measurement may require adjustment following this assessment.

If assessment against the criteria indicates that one of the two trials is feasible and the other infeasible, recruitment to the infeasible trial will stop. Only the trial for which recruitment has been feasible will continue. As we anticipate a higher incidence rate in the endometrial polyp trial, a lower than target recruitment rate would therefore still allow completion within the allocated project timescales.

At the end of the pilot phase, the Trial Steering Committee (TSC) will make a recommendation to the NIHR (funder) on whether the feasibility criteria have been met and whether the trial should continue. The TSC may report to the NIHR earlier if the trial meets the feasibility criteria below earlier than expected. Sheffield CTRU will aggregate feasibility of the research and intervention protocols based on the following criteria.

Table 1 Progression criteria for pilot to main trial

Domain	Target at 9m	Green	Amber	Red
Site set-up	30 centres setup and recruited and randomised at least one participant	25 or more centres recruited and randomised at least one participant	15-24 centres recruited and randomised at least one participant	Fewer than 15 centres recruited and randomised at least one participant
Participant recruitment	**Fibroids RCT** Average of 0.67 participants recruited per centre per month (approx. 117 in total) **Polyps RCT** Average of 1.3 participants recruited per centre per month (approx. 227 in total)	**Fibroids RCT** Minimum 80% of target (per centre per month) **Polyps RCT** Minimum 40% of target (per centre per month)	**Fibroids RCT** 60-80% of target (per centre per month) **Polyps RCT** 30-40% of target (per centre per month)	**Fibroids RCT** Below 60% of target (per centre per month) **Polyps RCT** Below 30% of target (per centre per month)
Number of women randomised to intervention (resection) and receiving resection treatment within three months of randomisation*	100% of intervention participants received intervention before 3 months post randomisation	80% of intervention participants received intervention before 3 months post randomisation. No change to timing of primary endpoint e.g. LBR at 15 months post randomisation.	Less than 80% of intervention participants received intervention before 3 months post randomisation. Consider a change to the primary endpoint point e.g. to 18 or 21 or 24 months post-randomisation	Not applicable.

Withdrawal from control treatment (receiving resection) before 6 months post randomisation	0% of control participants received intervention before 6 months post randomisation	Fewer than 10% of control participants received intervention before 6 months post randomisation	Between 10-50% of control participants received intervention before 6 months post randomisation	Greater than 50% of control participants received intervention before 6 months post randomisation

Note: Fulfilment of the 'green' criteria indicates continuation of the trial, fulfilment of the amber criteria indicates that steps should be in place to regain ground, fulfilment of the red criteria indicates the trial is not feasible.

* The primary endpoint is the LBR at 15-months post-randomisation; if in the pilot phase we find that fewer than 80% of the participants randomised to the intervention are receiving the treatment with 3-months of randomisation then we will consult with the TSC and DMEC about increasing the timing of the primary outcome to 18, 21 or 24 months post-randomisation. The LBR at 24 months post randomisation is already a secondary outcome.

Numbers of incorrect diagnosis/absence of abnormalities identified at surgery will be monitored during the internal pilot phase. Participant screening methods (section 5.3.1) may be modified if the proportion of participants identified as misdiagnosed is unacceptably high.

8.2 Primary outcome

1. Live birth rate (LBR) defined by the number of live births after 24 weeks gestation within the 15-month post-randomisation follow-up period relative to the number of women randomised. Multiple live births (e.g. twins) will contribute one event to the numerator in the calculation of the live birth rate. This will be assessed by either review of the participant's medical notes (if the patient is still receiving treatment from the centre/hospital in which she was randomised), or, if the patient has commenced treatment elsewhere or has been discharged, telephone contact with the participant will be performed by the Clinician/Research Nurse/Midwife/Associate PI/Dr.

   We have chosen 15 months post-randomisation as the cut-off for live births as this is potentially sufficient time for women in the intervention arm to have resection, conceive and give birth. It is possible that some women in the control arm may decide to withdraw

from their allocated treatment and undergo resection. However, in such cases we anticipate women would be unlikely to receive resection within 6 months of randomisation. This means that the estimated live birth rate up to 15 months follow-up in the randomised groups is unlikely to be confounded by the effect of women in the control arm undergoing resection. However, given the uncertainty around these estimates, the timing of the primary outcome will be reviewed as part of the progression criteria from pilot to main trial (see Table 1).

8.3 Secondary outcomes

Clinical outcomes

2. LBR at 24 months post-randomisation;
3. Time from randomisation to live birth (LBR);
4. Time from randomisation to pregnancy;
5. Clinical pregnancy (an observation of viable intrauterine pregnancy with a positive heart pulsation seen on ultrasound at/after 8 weeks gestation); miscarriage (spontaneous pregnancy loss, including pregnancy of unknown location (PUL), prior to 24 weeks gestation); premature labour (labour that happens before the 37th week of pregnancy); multiple birth (multiple live births per mother, e.g. twins or triplets etc.); still birth (delivery of a still born foetus showing no signs of life after 24 weeks gestation); and ectopic pregnancy rates (pregnancy outside the normal uterine cavity);
6. Detail of hysteroscopy received, including: number of hysteroscopic procedures received, duration of time post-surgery abstaining from sexual intercourse, type of resection performed (i.e. use of electrical energy device, morcellation devices and others). This applies to intervention arm only;
7. Patient satisfaction. A questionnaire will be designed with input from our PPI co-applicants and the Jessop Wing - Reproductive Health Research Public Advisory Panel to assess general patient satisfaction with the fertility treatments received since randomisation into the trial. The questionnaire will be sent to intervention arm participants and will concentrate on a) waiting time for treatment, b) satisfaction and tolerability of procedures received, c) thoughts on pre and post procedure information provided, d) psychological support, e) logistical family implications of surgery, f) procedure related anxiety;
8. Details of fertility treatments received, including details of medications received (e.g. clomid) and assisted reproductive techniques received (e.g. type of treatment, fresh or frozen cycle, quality and number of embryos transferred during IVF, IUI or ICSI cycle);

9. Incorrect diagnosis/absence of abnormalities at surgery. Where techniques other than diagnostic hysteroscopy have been used to visualise the endometrial polyp or submucosal fibroid, data will be collected regarding any false diagnoses of endometrial polyps/submucous fibroids;
10. Type of submucous fibroid (type 0, 1, or 2);
11. Number of participants in the control arm who undergo resection.
12. COVID-19 vaccination status (1st, 2nd, booster, approximate date and type of vaccine);

Safety outcomes

13. Adverse events due to procedure related and gynaecological/obstetric related complications (see section 10)

Health Economics

14. Health resource use of the participant measured at baseline, 6, 15 and 24 months post randomisation.
15. Patient costs measured following hysteroscopy for participants randomised to hysteroscopic resection
16. Cost per live birth gained.

8.4 Long term outcomes

1) Number of live births, miscarriages, terminations and still births,
2) Details of fertility treatment and;
3) Detail of hysteroscopic removal of submucous fibroids/endometrial polyps.

9. Assessments and study procedures

The schedule for data collection is summarised in Table 2. Data will be collected at specified time points from various sources including patient medical notes by **trained** members of the clinical research team and patient questionnaires, which may be completed in person, by post, by telephone/video call or online. Data collected directly by sites e.g. from medical notes, from the patient in person or by telephone/video call will be entered into the trial database by a trained member of the clinical research team. Every effort should be made to collect and enter data onto the database (Prospect) within +2 weeks of the due date (Directly post-hysteroscopy, 6, 15, 24 months +2 weeks). All contact attempts should be recorded on the database. When contacting the patient via the telephone a standard proforma ***(document: study proforma)*** will be used to

standardise the collection of information across all units. Data collected using the online system will be imported into the trial database by a member of the CTRU.

9.1 Study assessments schedule

Data will be collected at the time points listed below. Follow-up time points should be measured from the date of randomisation. A process flow diagram for data collection is provided in Appendix 1.

Eligibility assessment

Potential or fully eligible participants will be identified initially from medical notes and / or a database search. The site is required to follow the procedures used in their usual pathway for diagnosis and measurement of fibroids and polyps (see examples given in section 5.3.1).

Baseline

Following consent and prior to randomisation baseline data will be collected from participants. They will be asked a series of demographic, health resource use and COVID-19 vaccination status questions either in person during a clinic appointment, or by telephone / video call with a member of clinical research site staff. The questions may also be completed online. Data such as fertility markers, previous fertility treatments, type of infertility, miscarriage and detail of uterine abnormalities may be sought from the patient's medical records.

Intervention delivery – Hysteroscopic Resection

- Women randomized to the intervention arm will have the hysteroscopic procedure arranged as per local procedures.
- Following hysteroscopic resection fertility treatment will commence as planned

Directly Post-hysteroscopy (applies to the intervention arm only)

The clinical person performing the hysteroscopy procedure will be asked to complete a series of questions detailing the procedure which will be entered into the trial database. This will include details of the uterine abnormality (including size, grade and any misdiagnoses discovered during/after the procedure), any complications occurring during the procedure, detail of the techniques used (e.g. bipolar or monopolar resectoscopes, hysteroscopic morcellators or scissors or polyp snares), length of procedure and clinical staff involved. The site will also be asked to

record the number of pre- and post-operative appointments related to the intervention. These questions will apply to patients allocated to the intervention arm only.
Participants will be asked to complete:

A) the Patient Satisfaction Questionnaire (Document: Patient Satisfaction Questionnaire), which will ask questions about the patients' experiences of;

a) Waiting time for treatment
b) Satisfaction and tolerability of procedures received
c) Thoughts on pre and post procedure information provided
d) Psychological support
e) Logistical family implications of surgery
f) Procedure related anxiety.

B) the Patient Costs Questionnaire

These questionnaires can be completed either in person during a clinic appointment, by telephone / online, or video call with a trained member of site staff. The questionnaire may be sent directly to the participant from the CTRU via post or online.

Intervention follow-up

At 6 months post randomisation the research nurse/midwife will contact the patient to:

- Collect Adverse Events information
- Determine the length of time post-surgery abstaining from sexual intercourse

Additionally at 6 months, the research nurse/midwife/Associate PI/Dr will record the following information from patient medical notes and / or via telephone contact with the participant in line with CTRU SOPs;

- If pregnancy has occurred - time to pregnancy, pregnancy rate, miscarriage, ectopic pregnancy; adverse events; details of fertility treatments received and COVID-19 vaccination status.

The Health resource use questionnaire will be sent directly to the patient from the CTRU via post or online.

Treatment as usual - (No hysteroscopic resection)

Women randomised to 'treatment as usual' will continue with their fertility treatment as planned and will **NOT** receive the hysteroscopic resection.

Treatment as usual follow-up

At 6 months the research nurse/midwife/Associate PI/Dr will contact the patient to:

- Collect adverse event information.

- At 6 months post randomisation the research nurse/midwife/Associate PI/Dr will record the following (if applicable) from patient medical notes and / or via information collected from the telephone contact with the participant in line with CTRU SOPs; If a pregnancy has occurred - time to pregnancy, pregnancy rate, miscarriage, ectopic pregnancy; adverse events; details of fertility treatments received; and COVID-19 vaccination status.

The health resource use questionnaire will be sent directly to the patient from the CTRU via post or online.

Follow up at 15 and 24 months post-randomisation in both trial arms

15 months - Primary outcome

At 15 months post randomisation the research nurse/midwife/Associate PI/Dr will record the following information from the patients' medical notes and or via information collected from the telephone contact with the participant:

- The primary outcome (live birth rate)
- Time to live birth, time to pregnancy, pregnancy rate, miscarriage, premature labour, multiple birth, still birth, ectopic pregnancy, adverse events, details of fertility treatments received, COVID-19 vaccination status and health resource use.
- Adverse event information

The health resource use questionnaire will be sent directly to the patient from the CTRU via post or online.

24 month post-randomisation (and up to LPLV)

Members of site staff will be asked to record the following from patients' medical notes and / or telephone contact with the participant;

- Adverse event information
- Time to live birth, time to pregnancy, pregnancy rate, miscarriage, premature labour, multiple birth, still birth, ectopic pregnancy, adverse events, details of fertility treatments received and COVID-19 vaccination status.

The health resource use questionnaire will be sent directly to the patients from the CTRU via post or online.

Table 2 – Data collection time points

	Eligibility assessment	Baseline/ randomisation	Directly post-hysteroscopy #	6 months*	15 months*	24 months*	Post 24 months to Last Patient Last Visit (LPLV)	Long term (minimum 5 years post randomisation)
Demographics – age, fertility markers, previous fertility treatment received, type of infertility (infertility/recurrent miscarriage), BMI, smoking status.	MN	IP/MN						
Details of uterine abnormalities (size, grade)	MN	MN	MN					
Patient satisfaction			Q#					
Live birth rate (primary outcome)					T/MN (primary outcome)	T/MN		MN/NHSD
Time to live birth					T/MN	T/MN	MN	
Time to pregnancy				MN	T/MN	T/MN	MN	MN/NHSD
Pregnancy rate				MN	T/MN	T/MN	MN	MN/NHSD
Miscarriage				MN	T/MN	T/MN	MN	MN/NHSD
Premature labour					T/MN	T/MN	MN	

Multiple birth					T/MN	T/MN	MN	
Still birth					T/MN	T/MN	MN	MN/NHSD
Ectopic pregnancy				T/MN	T/MN	T/MN	MN	
Adverse events; obstetric, gynaecological or procedure related complications			IP/T/MN	T and MN	T and MN	T and MN	MN	
Obstetric outcomes				T/MN	T/MN	T/MN	MN	
Details of hysteroscopy received (intervention arm only)			MN	MN	MN	T/MN	MN	MN/NHSD
Details of fertility treatments received (clomid, IVF, IUI etc.)				MN	MN	MN	MN	MN/NHSD
Health resource use,		Q/MN		Q/MN	Q/MN	Q/MN		
Patient cost questionnaire			Q					
Time post surgery abstaining from sexual intercourse[#]				T/Q				
COVID-19 vaccination status (1st, 2nd, booster, approximate date and type of vaccine)		T/Q		T/Q	T/Q	T/Q	T/Q	

* Time points measured from randomisation

Intervention arm only

IP = in person, MN = medical notes

T = telephone contact with patient

Q = questionnaire, administered via post/email/online

NHSD = NHS Digital

Long term follow-up

Long term follow-up data will be collected 5 years after the final patient was recruited in one of two ways;

1) The clinic / hospital in which participants were randomised will be asked to check the medical records of those who gave consent for long term data collection. If the patient commenced treatment elsewhere, telephone or postal contact may be made with the participant by a member of the clinical research team.
2) An application will be made to NHS Digital requesting access to data from those who have agreed to this on the consent form. The names, date of birth and NHS number will be sent to NHS Digital for data linkage. Accessing data from NHS Digital is likely to result in increased data completeness compared to following up participants manually over this time frame, due to the likelihood of participants changing address and the risk of a low response rate (if followed up via questionnaire) or being discharged from the recruiting centre and receiving treatment/maternity care at another hospital (if followed up using local medical records).

9.2 Participant withdrawal from randomised treatment

Participants may wish to withdraw from the randomised study treatment i.e. women allocated to the control arm who later wish to undergo resection and women allocated to the intervention arm who later do not wish to undergo resection. There may also be a clinical need to withdraw participants from their randomised treatment allocation. In such cases centres will explain the importance of remaining in study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the trial. In such cases all study outcomes will continue to be collected. Nevertheless, if participants do not wish to remain in the trial their decision must be respected.

If the participant explicitly states their wish not to contribute further data to the trial, this is considered withdrawal from the trial, see 9.3.

9.3 Participant withdrawal from the trial

Participants may withdraw their consent for the trial at any time. If this occurs, this will be recorded in the CRF using the study completion / discontinuation form, in the trial database and on the trial withdrawal log. However, data collected up to the time of participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

Participants wishing to withdraw involvement (treatment and / or completion of questionnaires) will be asked to consent to use of data from their medical records.

9.4 Loss to follow-up

Participants will be defined as lost to follow up if they have not been contactable, despite all reasonable efforts, at the point of final data collection (24 months post randomisation). If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form. Data about pregnancy outcomes and whether hysteroscopic removal of submucous fibroids or endometrial polyps were removed for participants lost to follow-up will be sought directly from medical notes.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Table 3 - Adverse Event and Serious Adverse Event information

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. *(refer to SOP PM004 Adverse Events and Serious Adverse Events for more details)*
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death ● Is life-threatening* ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation** ● Results in persistent or significant disability or incapacity ● Is a congenital anomaly/birth defect ● Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**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, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and up to completion of the 24 month follow-up by the last participant recruited (LPLV).

Hysteroscopic resection of submucous fibroids and endometrial polyps is a routine procedure for which the side effects are understood. Therefore, only those AEs which are deemed serious or of particular relevance to the procedure will be recorded / reported in this trial. These are listed as 'expected AEs' in Table 4.

Adverse Events

Participants will be asked for any details of adverse events, at four time points up to the participants' final study related follow-up event; post procedure (if randomised to receive hysteroscopic resection of submucous fibroids or endometrial polyps), then at 6, 15 and 24 months post randomisation. AEs or SAEs may also be identified by the Research Nurse/Associate PI/Dr, or any other individual, at any point during the study, up to last patient last visit.

When an event is identified the process for recording and reporting outlined in Figure 5 will be followed. The local PI (or other suitably trained member of research staff, if the task is delegated to them) should be notified immediately and assess the event for classification as an SAE (see definition in section 10.1).

AEs confirmed as NOT serious will be checked against the list of expected AEs (Table 4).

<u>Expected AEs</u>

AEs which are expected will be recorded by site staff in the participant CRF.

<u>Unexpected AEs</u>

AEs which are not expected will not be recorded on the basis that hysteroscopic resection of submucous fibroids and endometrial polyps is a routine procedure, for which the side effects are understood. We do not anticipate any AEs, which are of relevance to the intervention, other than those listed in Table 4, unless the site PI considers the events to be significant.

Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

Table 4 - Expected Adverse Events

Gynaecological / obstetric related	**Procedure related (immediate)**	**Procedure related (delayed)**
●Placenta accreta, increta, percreta ●Placenta abruption ●Growth retardation ●Foetal distress ●Antepartum haemorrhage ●Post-partum haemorrhage ●Placenta Praevia (grade 3 & 4) ●Placental abruption ●Manual removal of placenta	●Uterine perforation ●Bowel injury ●Bladder injury ●Significant bleeding during the procedure resulting in additional intervention ●Air embolism (though this is very rare and more commonly associated with resection of Type 2 submucous fibroids) ●Fluid overload and hyponatremia ●Vasovagal reaction (hypotension and fainting) requiring additional intervention during the procedure (e.g. presence of anaesthetist) OR after the procedure ●Return to theatre immediately	●Post-operative adhesions requiring intervention ●Infection

Serious Adverse Events

All AEs classed by the PI or delegate as serious will require more detailed information to be recorded in the participant CRF. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event (see section 10.4).

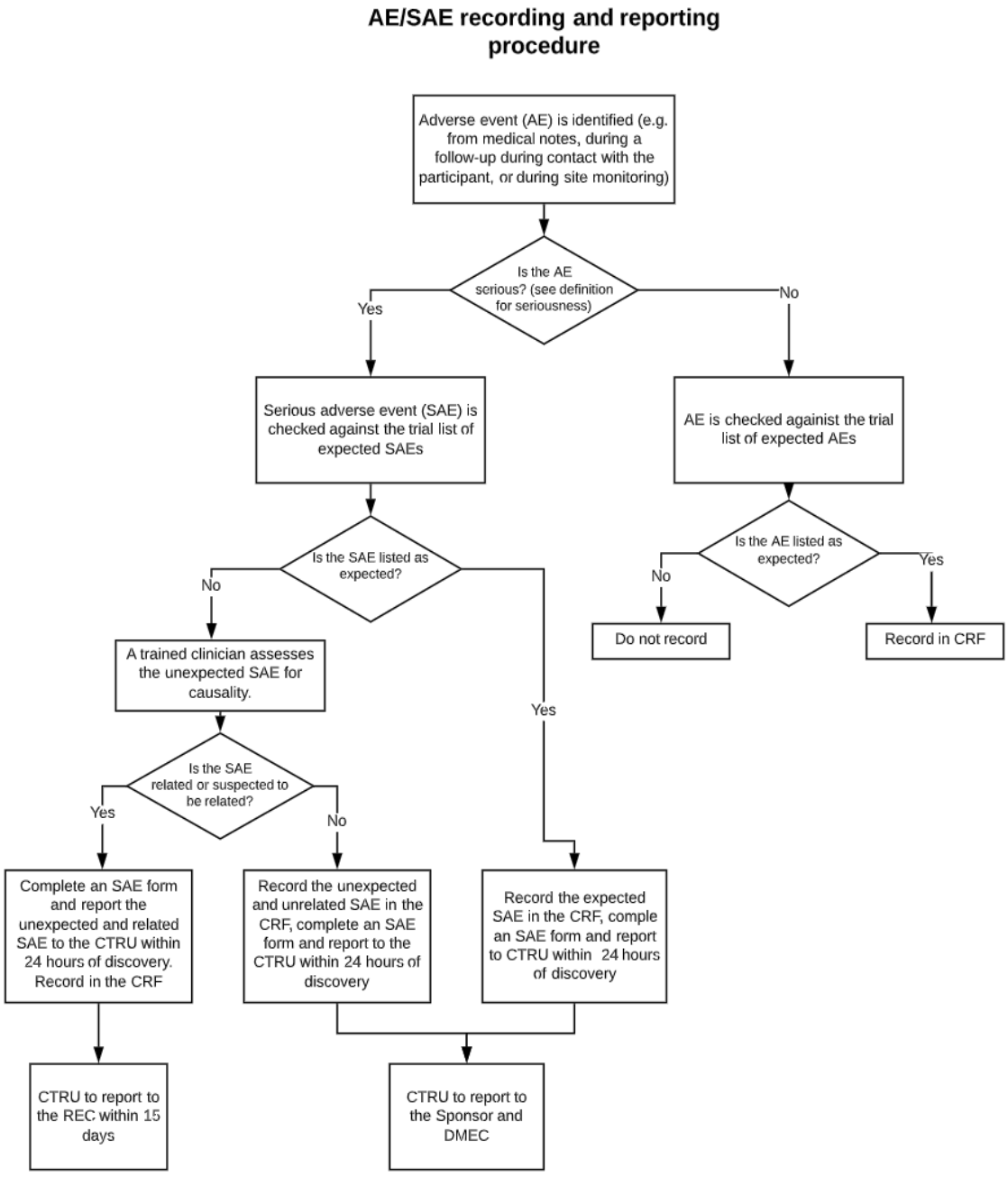
Expected Serious Adverse Events

Expected SAEs are those events listed in Table 4 which are assessed as serious using the definition in section 10.1.

Unexpected Serious Adverse Events

All unexpected serious adverse events should be assessed for causality by the PI or delegate. Following reporting of these events within 24 hours by site staff to the CTRU, all unexpected SAEs will be reported by the CTRU to the sponsor and DMEC. SAEs which are unexpected and related / suspected to be related to the intervention will be reported further by the CTRU to the REC within 15 working days.

Figure 5 - Recording and reporting of AEs and SAEs



10.3 Study specific exemptions

For women who become pregnant during the trial exemptions include any event during the birth/birth process that relates to the process of delivery (e.g. hospitalisation for normal vaginal delivery, planned C-section, episiotomy etc.) will not be recorded as an AE or SAE (information regarding miscarriage and emergency C-sections will be collected on the CRF).

10.4 SAE recording and notification procedure

All SAEs should be reported to the CTRU within 1 working day from the point of identification.

Sites should try and enter a diagnosis into the reporting form. If a diagnosis is unknown at the time of submission to CTRU, the form may be updated at a later date.

SAE notification procedure

- Sites should notify Sheffield CTRU of all unexpected SAEs immediately but within a maximum of 1 working day from the point of identification. Congenital anomalies and neonatal deaths will be reported using the study database as soon as possible after the event is identified.
- Details will be recorded on a SAE form (filed in the Investigator site file or downloaded from the AE eCRF page) and can be sent to the Sheffield CTRU via the following methods:
    - **Email:** Completed SAE report forms should be emailed to the dedicated email address (ctru-saes-group@sheffield.ac.uk). The email account will be checked during office hours (between 9am and 5pm Monday to Friday).
- In the event that no clinical assessment can be made immediately, it is recommended that the SAE form is sent to the CTRU regardless, and an assessment is obtained as soon as feasible on a new SAE form and forwarded to the CTRU in Sheffield.
- Follow-up or corrections to information should also be reported on a new SAE form and forwarded to the CTRU in Sheffield.
- Sheffield CTRU will be responsible for reporting SAEs to the sponsor, the DMEC and the REC.

All SAEs will be reviewed by the DMEC at regular intervals. The CI will inform PI's concerned of relevant information that would adversely affect the safety of the participants.

10.5 CTRU responsibilities

The Sponsor usually delegates CTRU responsibility for the reporting of SAEs to the regulatory authorities and the research ethics committee, as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

11.1 Sample size

The primary outcome for both trials will be live birth rate (LBR) defined by the number of live births after 24 weeks gestation within the 15-month post-randomisation follow-up period relative to the number of women randomised.

Our review of the research literature including a Cochrane review of hysteroscopic removal of submucous fibroids and endometrial polyps (6) has found no reported estimates of the LBR in our proposed target populations. Although, two previously conducted RCTs included in the Cochrane review roughly indicate a doubling of pregnancy rates. The first quoted a clinical pregnancy rate (at 6-7 weeks) of approximately 214/1000 (21%) over 12 months in a sample of 42 women with fibroids (submucosal and mixed submucosal intramural) without surgery and a miscarriage rate (between 7 and 12 weeks) in those without surgery of approximately 556/1000 (56%) (35). Applying the miscarriage rate to the pregnancy rate (i.e. 0.21 * 0.56) would give a LBR of approximately 10% over 12 months in the control arm (no resection). The second, in women with endometrial polyps undergoing IVF, detected an increase of pregnancy rates from 28% to 63%, with no miscarriage rate reported (36). We therefore estimate a usual care LBR of 10% within 15 months in the populations of women proposed for inclusion in this study, both for the submucous fibroid and endometrial polyp RCTs.

Assuming a 10% LBR in the no hysteroscopic removal (control) group and that an absolute increase of 10%, to a 20% LBR (a relative risk of 2.00) in the hysteroscopic removal (intervention) group is of clinical and practical importance. Then to have a 90% power of detecting this difference or more, in LBR rates between the groups, as statistically significant at the 5% two-sided level, will require 266 women per group (532 in total). Adjusting for a predicted attrition rate of 5% (due to potential difficulties of follow-up for patients who have been referred from other NHS Trusts) we will require 560 participants to be randomised.

A similar sample size will be required for RCT2 (polyp population) i.e. 560 participants, so a total of 1120 participants are required for RCT1 and RCT2 combined.

We will verify the 10% control group LBR used to inform the sample size calculation by conducting two interim assessments. The first interim analysis will be undertaken using the clinical pregnancy outcome once 50% of the target number of participants have been randomised. The clinical pregnancy outcome can be regarded as a proxy or surrogate outcome for the primary outcome the live birth rate, and allows for an earlier interim assessment to be made.. If the clinical

pregnancy rate outcome is greater than or equal to 10% we will continue to the 2nd interim assessment, using the primary outcome variable.. If the clinical pregnancy rate outcome is less than 10%, then the DMEC will then make a recommendation to the TSC regarding any need to alter the sample size of one or both of the trials.

Note: Clinical pregnancy rate is defined by an observation of viable intrauterine pregnancy with a positive heart pulsation seen on ultrasound at/after 8 weeks gestation

The 2nd interim assessment will be undertaken once 50% of randomised participants have been followed up for 15 months. With live birth data on approximately 50% (280/560 women per trial) we will be able to estimate the LBR within +/5% (i.e. 95% CI: 5% to 15%). As we anticipate the endometrial polyp trial will recruit quicker than the submucous fibroid trial, and the control group LBR rate may differ between these two populations, this assessment will be undertaken in the two trials separately, at different time points. Both interim assessments will be undertaken by the DMEC, who will then make a recommendation to the TSC regarding any need to alter the sample size of one or both of the trials.

11.2 Statistical Analysis

Data from the two trials will be analysed and reported separately. Both trials have the same primary and secondary outcomes so the analysis and reporting will be similar. As both trials are pragmatic parallel group RCTs, data will be reported and presented according to the latest CONSORT guidelines. The statistical analyses will be performed on an intention-to-treat basis. Under the strict intention to treat (ITT) principle, all women will be included in the analysis once they are randomised as per the allocated treatment regardless of what happens after randomisation. All statistical exploratory tests will be two-tailed with alpha = 0.05.

Interim Analysis

There is no formal planned interim analysis other than the assessment of recruitment, treatment uptake and withdrawal from randomised treatment allocation after the 9-month internal pilot phase, and the assessments of clinical pregnancy and live birth rates in the control arm after 50% of randomised participants have been randomised and followed up for 15 months, respectively.

At the first interim assessment, the clinical pregnancy rate will be calculated in the control arm. If lower than the 10% estimate used for LBR in the control arm in the sample size estimation, sample size re-estimation will be considered, under the guidance of the DMEC. If greater than or equal to 10%, no adaptation will be made and the next interim assessment will take place when 50% of participants have completed the 15-month follow-up.

At the second interim assessment we shall calculate the LBR and its associated 95% CI for participants in the control arm. If the CI includes the 10% LBR (which we assumed for the control group in the sample size calculation) then we will continue to recruit to the original target sample size.

If the CI for the LBR in the control arm does not include 10% then we will re-estimate the sample size using the point estimate for the LBR we have observed thus far in the control arm and the same target difference of 10%. If this results in a reduction in the target sample size we will continue to recruit to the original target sample size (of N=560). If this results in an increase in the target sample size we will seek the opinion of the independent DMEC and TSC about increasing the sample size.

Baseline assessments

Baseline summary statistics will be reported by treatment arm and overall. Comparability between treatment arms (at randomisation or before interventions) will be descriptively reported without any statistical significance testing. Any observed differences in baseline characteristics and demographics believed to be important in confounding effectiveness evaluation of the intervention will be descriptively reported and adjusted for during sensitivity analyses described below.

Analysis of primary outcome

The primary outcome is the Live birth rate (LBR). This is a defined by the number of live births after 24 weeks gestation within the 15-month post-randomisation follow-up period relative to the number of women randomised. Multiple live births (e.g. twins) will contribute one event to the numerator in the calculation of the live birth rate. The denominator for calculating the LBR will be the number of women randomised to each group. The primary binary outcome, the live-birth rate (LBR), will be compared between the two groups (hysteroscopic removal of submucous fibroids and endometrial polyps (Intervention) and no hysteroscopic removal (control)) using a Chi-squared test. A 95% confidence interval (CI) for the risk difference (RD) in LBR between the groups will also be calculated (37) using the recommended Wilson method. In consonance with the CONSORT guidance (38), the primary outcome will also be reported as maximum likelihood estimate (MLE) of the OR (Odds Ratio) with associated 95% CI based on a simple logistic regression model with the randomised group as the only predictor.

A complementary adjusted analysis will be undertaken using a multiple logistic regression model to account for stratification factors (centre and history of infertility/recurrent miscarriage) and potential confounding factors imbalanced at baseline. These variables will be treated as fixed

factors in the multiple logistic regression model. An adjusted MLE of the OR with associated 95% CI and p-value will be reported, to support the unadjusted results. Again, in consonance with the CONSORT guidance, the adjusted MLE of the RD will be estimated adjusted for randomisation stratification factors and covariates described above using one of the following approaches depending on convergence and model fitness;

i. a Generalized Linear Model (GLM) (39) either with a Binomial or Poison distribution and log link function through estimation of margins (40),

ii. a GLM either with a Binomial or Poison distribution and identity link function (41).

In either case, a GLM with a Binomial distribution will be the first choice. In the case of a GLM with a Poison distribution, robust adjusted standard errors will be used (39–41).

Any noted differences between the unadjusted and adjusted primary analyses will be highlighted.

Missing primary outcome data

A default conservative 'worst case' scenario will be adopted as the primary approach for all the analyses, unless stated otherwise. Here, a woman whose live-birth outcome is unknown for some reason(s) contribute to a negative outcome, that is, they shall be assumed to have failed to produce a live birth. Due to multiple pregnancy, there is a possibility that some pregnant women may achieve multiple births resulting in potential multiple live births outcomes from a single mother. The default approach for dealing with multiple births for the primary analysis will be that a live birth is counted as a single event regardless of how many babies are born during that live birth.

A sensitivity analysis for the primary outcome, LBR, with missing birth outcome data, will be imputed through a "best" case (i.e. assume the woman had a successful live birth) and multiple imputation with chained equations and the results compared with the default analysis.

Non-compliance and contamination

Further sensitivity analysis for the primary outcome, LBR, will be undertaken to adjust for non-compliance and contamination (i.e. use of treatment by individuals in the control arm) using methods described in Cuzick et al (42) and the results compared with the default ITT analysis.

Analysis of secondary outcomes

Secondary binary outcomes such as the LBR at 24 months, multiple birth rate, implantation rate, clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate, pre-term delivery rate and still

birth rate will be analysed in a similar way to the primary outcome. The denominator for the calculation of the rates will be number of participants randomised to the intervention and control arms respectively. We shall also repeat the above analyses on the per protocol population.

The ITT population (and safety) populations will consist of all women who consent and are randomised to receive or not receive hysteroscopic removal of submucous fibroids or endometrial polyps.

The per protocol population for those randomised to receive hysteroscopic removal of submucous fibroids or endometrial polyps is defined as a patient a) attending the clinic for the hysteroscopic excision of submucous fibroids and or endometrial polyps and b) receiving the procedure per protocol (following the sites usual procedures for hysteroscopic removal of submucous fibroids and / or endometrial polyps) within the first six-months post-randomisation. The PP population for those randomised to the control group and not to receive hysteroscopic removal of submucous fibroids or endometrial polyps is defined as a patient a) attending the clinic and b) not undergoing hysteroscopic removal of submucous fibroids or endometrial polyps procedure per protocol within the first six months post-randomisation.

Safety and adverse events

Adverse events including serious adverse events (death; hospitalization (initial or prolonged); disability or permanent damage; other important medical events), will be reported for each randomised group and compared between the two groups using a Fisher's Exact test or Chi-squared test (as appropriate). A 95% confidence interval (CI) for the difference in adverse event rate between the groups will also be calculated.

Sub-group analyses

An exploratory sub-group analysis using multiple logistic regression, with the primary outcome LBR, will look for an interaction between treatment group and the following sub-groups: a) infertility/recurrent miscarriage and b) type of fertility treatment received. A sub-group analysis looking at interaction between treatment group and type of submucous fibroid may be carried out if a sufficient number of control participants undergo diagnostic hysteroscopy, as part of site's usual diagnostic procedures, with fibroid type identified.

Analysis of time to event outcomes

Within the main trial period all women recruited to the trial will be followed up for a minimum of 2 years post-randomisation. Given the study recruitment will take 2.5 years then the first recruited women will have up to 4.5 years follow-up. Women will be censored at the last known date of follow-up if they have not had a live birth/clinical pregnancy.

Intervention waiting times and withdrawal from randomised treatment

The primary outcome analysis (the LBR at 15 months post-randomisation) may be affected by withdrawal or by women not receiving the randomised treatment allocation. That is if participants randomised to the intervention do not receive the resection by approximately 3-months post-randomisation we may not have a valid, reliable, and robust estimate of the effect of actually receiving the intervention. Rather we will just have an estimate of the policy of randomising participants to receive resection or not. Similarly, if participants randomised to the control treatment withdraw from the control treatment and receive a resection in the first 6-months post-randomisation then again we will not have a valid reliable and robust estimate of the effect of not receiving the intervention. If a substantial proportion of participants withdraw before 6 months post-randomisation or do not receive their treatment allocation by 3-post-randomisation then in these circumstances the comparison of the LBR outcome at 15 month post-randomisation outcome between the randomised groups may not produce a reliable and valid estimate of the effect of resection of fibroids / polyps or not.

The secondary outcome of time to live birth could also be affected by this. Statistical adjustment methods such as rank preserving structural failure time models and inverse probability weighting (IPCW) will be used to adjust for potentially informative withdrawal from randomised treatment (or withdrawal from the trial) in secondary analyses of the end of trial follow up data. These methods have been shown to perform well in a range of scenarios related to informative drop-out such as treatment crossover, though are associated with limiting assumptions (43–45). A subgroup analysis will include women with infertility/recurrent miscarriage. We also expect that IVF could be important and may differ between treatment arms. If this is the case we will undertake an analysis adjusting for IVF to estimate the relative effectiveness of surgery vs no surgery in the absence of IVF, using inverse probability of censoring weights.

Analysis of long term outcomes

We will also collect long term follow-up data from medical notes and / or NHS Digital for each participant after the trial has ended (minimum 5 years after each participant consented). The following data will be collected: number of live births; number of miscarriages; number of still births; number of terminations; whether or not the participant received hysteroscopy for endometrial polyps/submucous fibroids. The analysis of the count outcomes such as number of live births per single mother will be tabulated by treatment group to explore its distribution. The number of live births per single mother will be modelled as counts using either a Generalized Linear Model (GLM) with a log link function and: Poisson distribution or, Negative Binomial distribution in the presence of over dispersion; with the length of follow-up included in the model as an exposure variable. The mean incidence of live births per mother, Incidence Rate (IR), in

each treatment group over the study duration will be reported. The intervention effect will be reported as Incidence Rate Ratio (IRR) with associated 95% CI and P-value. An adjusted analysis will be undertaken to account for stratification factors (centre and history of infertility/recurrent miscarriage) and potential confounders, depending on the observed imbalance between treatment groups. The adjusted mean incidence of live births per mother, adjusted Incidence Rate (aIR), in each treatment group over the study duration will be reported. The intervention effect will be reported as adjusted Incidence Rate Ratio (aIRR) with associated 95% CI and P-value.

Health economic evaluation

The primary cost-effectiveness analysis will present costs per extra live birth, comparing the surgical interventions to control taking an NHS and personal social services perspective in accordance with NICE guidelines (46). Extra live birth will be used as the outcome instead of quality adjusted life years (QALYs) because QALYs are intended to capture improvements in health, not for placing a value on additional lives (47), as recognised in the NICE Clinical Guideline for Fertility (25). Resource use will include the intervention costs for hysteroscopy, expectant management costs, costs of IVF/IUI treatments and for those who conceive antenatal and post-natal visits, delivery costs and any hospital stays not related to birth for both mother and baby. Patient centered costs related to time taken to travel to appointments to receive the intervention (and the loss of productivity associated with attending such appointments), non-NHS funded fertility treatments, and for those who conceive antenatal and post-natal visits will also be collected for use in a secondary analysis that will take a societal perspective. Women will be asked to complete a resource use questionnaire at baseline, 6, 15 and 24 months post randomisation – each questionnaire will ask for data from the preceding 3 months. Women in the hysteroscopy arms will be asked to complete a patient cost questionnaire following their hysteroscopy for information only relating to their hysteroscopy. Unit costs will be derived from appropriate national sources and will include NHS reference costs and Personal Social Service Research Unit costs (48,49). The resource use questionnaire will be designed for this study and will draw on data collection tools developed in ScHARR and those collated by the Database for Instruments for Resource Use Measurement (DIRUM). Two sets of economic analyses will be conducted – one based on an intention-to-treat analysis of the trial data, and another based on an analysis that adjusts for potentially informative withdrawal of randomised treatment or trial withdrawal. Results will allow for uncertainty using bootstrapping and probabilistic sensitivity analysis.

12. Trial supervision

12.1 Trial Steering Committee

The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources, consider recommendations from the DMEC and make recommendations on closing the trial prematurely. The TSC will meet at regular intervals, as defined in the TSC terms of reference. The TSC memberships includes an independent Chair, clinical and statistical expertise and PPI representation.

12.2 Data Monitoring and Ethics Committee

The DMEC will review monthly reports provided by the CTRU to assess the progress of the study, safety data, the critical endpoint data as required and will review the statistical analysis plan. The DMEC will meet at regular intervals, as defined by the DMEC charter and make recommendations to the TSC or funder, including whether the trial is stopped or modified on the basis of data / on safety grounds.

12.3 Trial Management Group

The trial will be supervised on a day-to-day basis by the Trial Management Group (TMG). This group reports to the TSC. At each participating centre a local Principal Investigator will report to the TMG via the staff at the Sheffield CTRU.

The core TMG will meet regularly at least once every two months but rising to at least once per month before key milestones (ethical approval, recruitment initiation etc.). In addition, investigator meetings will be set up during the recruitment phase of the study, at least once every two months, where the site PIs (or another delegated individual) will discuss pertinent issues with the research team, including recruitment, data completion and intervention delivery.

13. Data handling and record keeping

Participant confidentiality will be respected at all times during the study. Data will be collected and handled in line with CTRU Standard Operating Procedures and in accordance with NHS Trust policies at Sheffield Teaching Hospitals NHS Foundation Trust and at each participating site. This will ensure systems are in place to protect confidentiality of participants and the systems are secure.

Patients will be allocated a unique identification number that will be used to identify them throughout the trial. This will be recorded on all data collection forms to preserve pseudonymity

(except where identifiable information is collected, such as on the contact details form, which will be kept separately).

All consent forms and questionnaires will be kept in a locked filing cabinet in a secured area and will be retained for a minimum of 5 years after study completion, in accordance with the sponsor's archiving requirements.

Sheffield CTRU may request consent forms to be sent from the research site to the CTRU via post or email as part of remote monitoring procedures. Participants will be asked to consent to this in the study consent form.

Data will be entered on to a secure study database, hosted on University of Sheffield servers and accessible over the internet, which adheres to data protection and NHS regulations. Identifiable data, including names, addresses and dates of birth, will be shared with Sheffield CTRU to allow for participant follow-up. Consent will be obtained from the patient for this to occur.

13.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above. Archiving of the site files and participants' records at each participating centre will be the responsibility of the local R&D Department.

14. Data access and quality assurance

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from CTRU (study manager, research assistant, data managers, lead & Senior Research Nurses), the sponsor and host organisations to permit study related monitoring, audits and inspections. Select CTRU staff will have access to personal data including names, addresses, phone numbers and email addresses in order to undertake the questionnaire follow-up. In addition to this, access to the eCRF and questionnaire data will be required for study monitoring and audit purposes. A study monitoring plan will be devised in accordance with the Sheffield CTRU SOPs on Trial Monitoring (QU001).

The study database resides on Sheffield CTRU's in-house data management system. All data transmissions are encrypted using SSL/TLS, and access to the system is controlled by usernames and encrypted passwords. A comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. The database will incorporate quality control procedures to validate the study data. Discrepancy reports will be generated to highlight missing and erroneous information.

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the study sponsor. All paper documents will be stored securely and kept in compliance with the Data Protection Act (2018). Data entered onto the study database will be stored on CTRU servers at the University of Sheffield on behalf of the sponsors. After the trial has been completed and the reports published, access to the data will be strictly controlled.

14.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital or clinic at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

14.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central and/or on-site monitoring (including Pharmacy if applicable) will be undertaken at a level appropriate to the detailed risk assessment and will be documented in the Site Monitoring Plan (SMP).

14.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial, or the protocol relating to the trial, which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and, for CTIMPs, the MHRA in writing within 7 days of becoming aware of a serious breach.
All serious breaches and protocol non-compliances should be reported to CTRU, in-line with CTRU SOP PM011 and within 24 hours of site staff becoming aware.

14.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed either on-site or carried out remotely for each participating site before each site recruits their first participant. During this visit/remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Site monitoring may be performed either on site or remotely and will occur throughout the study as specified in the Site Monitoring Plan. Additional monitoring or on-site visits will be undertaken where required. During monitoring, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact and / or visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

A close-out review may be done remotely or by an on-site visit after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

14.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to post consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

15. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The anonymised data will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, will be documented in a Publication and Dissemination Plan.

16. Finance

Research funding has been obtained from the National Institute for Health Research Health Technology Assessment Program.

17. Ethics approval & regulatory compliance

Before initiation of the study at participating site, the protocol, ICFs and information materials to be given to the participants will be submitted to West Midlands – Edgbaston Research Ethics Committee. Any further amendments will be submitted and approved by the HRA and ethics committee before sharing with and implementing at sites.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

Hysteroscopic removal of submucosal fibroids and endometrial polyps is used in routine clinical practice for patients with infertility and recurrent miscarriage. Therefore, we do not anticipate any significant ethical issues with the use of an already widely used procedure. However, women may feel disappointed should they be randomised to the control arm of the trial. As such, the information that will be provided verbally and through an information sheet, which will be developed in consultation with patients and representatives of the patient involvement group, will be designed to ensure that it is presented in a sensitive way whilst explaining the nature of the trials randomised design. The information sheet clearly explains the participation in the trial is voluntary with the option of withdrawing at any stage and the participation or non-participation will not affect their usual care. Only Individuals who are NHS employees (substantive or honorary) and who have access permissions will examine hospital databases for potentially eligible participants.

17.1 Training for site staff involved in participant recruitment

Prior to the start of recruitment, recruiting centres will attend an “investigator meeting” where training will be provided on the trial protocol and specifically on the recruitment and consenting process. Attendees will also be shown the participant recruitment video. Training will be based on recommendations from previously undertaken surgical trials as well as previous trials in this specific patient population that this team has successfully completed (50–53).

As well as providing the specific training, a checklist will also be provided to centres, listing the above and other relevant recommendations, to be used during recruitment conversations with potential participants. At the training event, recruitment strategies will be discussed with the attendees (including PPI representatives) and the checklist may be altered as a result.

18. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, ICFs, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of Confirmation of Capacity and Capability (CCC) has been issued.

19. Trial Organisation and Responsibilities

19.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

COVID-19

Site PIs will be responsible for ensuring that local policies and procedures are followed in relation to the COVID-19 pandemic.

19.2 Nursing co-ordinator each site

Each participating centre should delegate a Research Nurse/Midwife/Associate PI/Dr as the local Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, and that patients are provided with study information sheets and given the opportunity to discuss the study if required. The research nurse/midwife/Associate PI/Dr may be responsible for the collection of data and follow-up evaluations.

19.3 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework

for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Study Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

20. Patient & Public Involvement (PPI)

During the outline and full stages of this grant application for this trial, women who had experienced resection of submucous fibroids and endometrial polyps during their fertility journey were asked for their comments. The study was reviewed by The Reproductive Health Research Public Advisory Panel (PPI) at the Jessop Wing - Sheffield and the PPI co-applicants. We have PPI representation on the TMG, which meets at least once every two months plus PPI representation on the TSC, which will meet every six months. Guidance and advice will be sought throughout the course of the trial including requesting PPI input into the development of participant facing materials.

21. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment that is provided. Non-NHS sites will be asked to provide evidence of indemnity as part of the site set-up process.

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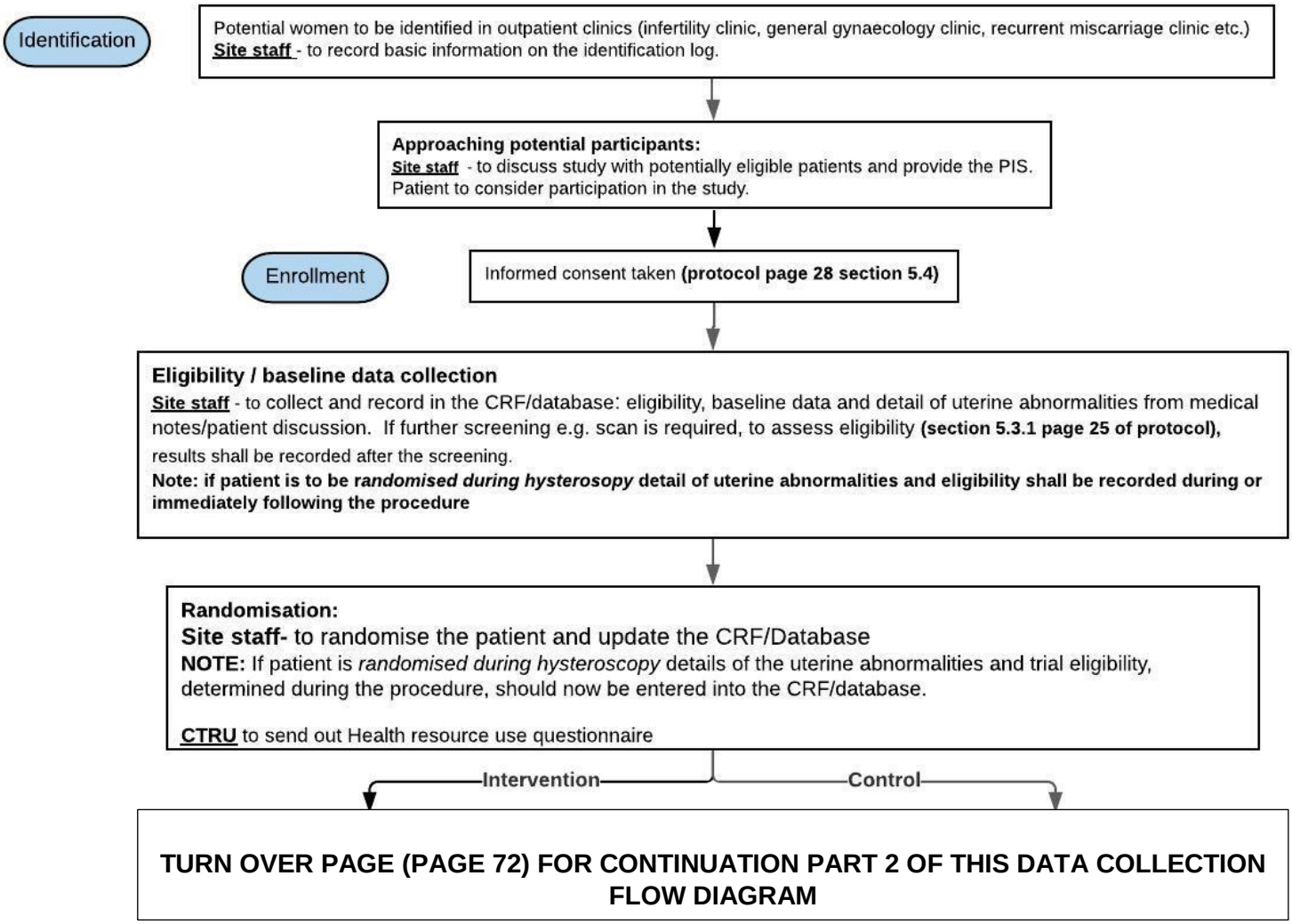
Appendices

Appendix 1 Process flow diagram for data collection

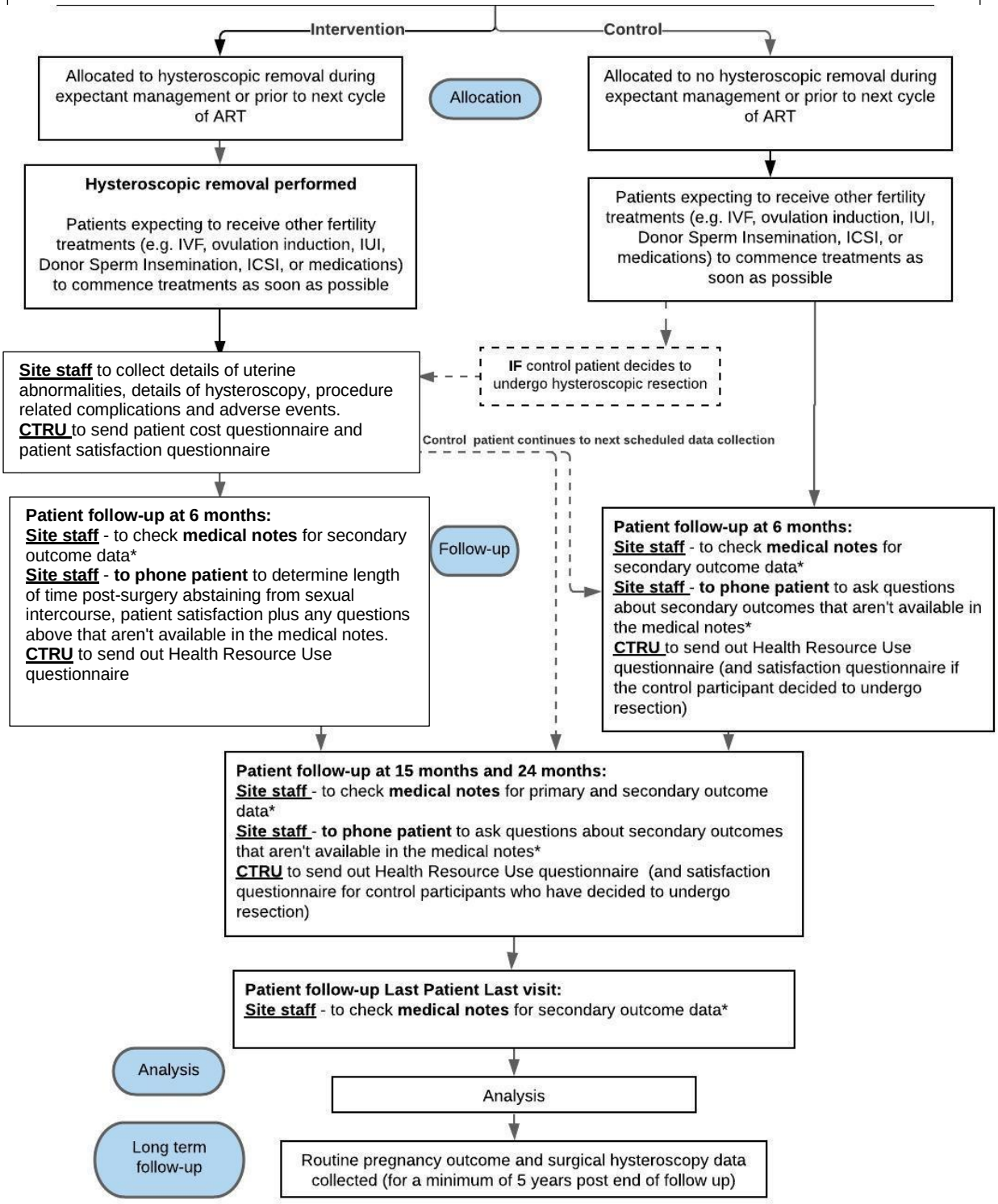
Part 1 Participant Identification to Randomisation



Process Flow diagram continued…

Part 2 Participant allocation to 5 year data collection

SEE PREVIOUS PAGE 71 FOR EARLIER PART 1 DATA COLLECTION STEPS FROM PARTICIPANT IDENTIFICATION TO RANDOMISATION



*See data collection schedule in Table 2 on pages 41-42 of the trial protocol