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Synopsis

# Removal of small fibroids and polyps in patients with infertility and recurrent miscarriage: The HELP Fertility? RCT

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## Abstract

**Background:** Infertility affects one in six of females globally, with uterine submucous fibroids and endometrial polyps being common findings. The effectiveness of surgical removal to improve fertility remains uncertain. The associated surgical risks and costs highlight the need for more robust research in this area.

The HELP Fertility? Study aimed to assess the clinical and cost-effectiveness of hysteroscopic removal of endometrial polyps and submucosal fibroids, compared to no removal, in improving fertility outcomes for participants with infertility or recurrent miscarriage while also evaluating participant experience and longer-term effects.

The trial was designed as a multicentre, pragmatic superiority randomised controlled trial with two concurrent trials; one for endometrial polyps and one for submucosal fibroids, with a 9-month feasibility pilot. Participants were randomly assigned 1 : 1 to either receive hysteroscopic resection or no resection. The primary outcome was live birth rate at 15 months. Secondary outcomes included pregnancy rates, procedure details, patient satisfaction and resource use.

**Results:** COVID-19 resulted in significant recruitment challenges, with delays in site set-up and participant enrolment due to pandemic-related healthcare disruptions. The trial was closed early by the National Institute for Health and Care Research–Health Technology Assessment programme following recruitment of 35 participants (19 hysteroscopic resection and 16 no resection) out of a target of 1120.

The clinical and cost-effectiveness analyses were severely limited by the small sample size. Clinical pregnancy rates within 15 months of randomisation were 26.5% (5/19) in the hysteroscopic resection group and were 37.5% (6/16) in the no resection group. The live birth rate within 15 months of randomisation (the primary outcome) were 15.8% (3/19) in the hysteroscopic resection group and 18.8% (3/16) in the no resection group: a risk difference of −3.0% (95% confidence intervals −31.1% to 24.2%). No serious adverse events were observed in the follow-up.

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At the mean, hysteroscopic resection resulted in fewer live births, but increased costs, implying that resection is not cost-effective compared to no resection. However, results were highly uncertain and confidence intervals for incremental costs and the incremental live birth rate spanned zero. At a cost-effectiveness threshold of £20,000 per additional live birth, there is a 10% probability that hysteroscopic resection represents a cost-effective intervention and a 90% probability that no resection is cost-effective. There is a 56% probability that resection is more costly and less effective than no resection.
Despite implementing remote training, centralised support and opening 16 National Health Service sites by February 2023, insufficient participants were recruited within planned time frames. The study was ultimately closed as part of the NIHR Research Reset Programme in February 2023.
**Limitations:** With recruitment of 35 participants against a target of 1120 and the follow-up period limited to 15–24 months, the results of this study are limited.
**Conclusions:** The HELP Fertility? Trial faced recruitment challenges, enrolling only 35 participants. Due to the small sample size, researchers could not statistically determine any significant difference in live birth rates between surgical intervention and no resection for small fibroids and polyps. Cost-effectiveness results should be interpreted with caution. Researchers were able to provide valuable insights into clinical research complexities, which include clinician and patient equipoise.
**Future work:** The research highlights several critical considerations for future fertility studies.
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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GJMM1915.

## Introduction

This report discusses the work conducted on the Hysteroscopic Excision of Leiomyoma and Polyp in Infertility: Two Randomised Controlled Trials ('HELP Fertility?') study. The study investigated the clinical and cost-effectiveness of hysteroscopic removal of small submucosal fibroids and endometrial polyps compared to no hysteroscopic removal in participants presenting with infertility or recurrent miscarriage. This study was developed in response to a call by the National Institute for Health and Care Research (NIHR)–Health Technology Assessment (HTA) programme.

The study had difficulty recruiting sufficient participants to reach a target of 1120. The trial was closed to recruitment early after 35 participants were randomised.

### *Rationale for research and background*

Infertility is listed as a global public health issue, experienced by approximately one in six people worldwide.[1] In the UK, in 2022, over 52,000 patients were recorded as receiving in vitro fertilisation (IVF) at Human Fertilisation and Embryology Authority licensed fertility centres, with live birth rates (LBRs) from fresh embryo transfers averaging at 30% in preliminary data.[2] Both naturally conceived pregnancies and those resulting from assisted conception can unfortunately result in miscarriage, reported to affect between 10% and 50% of females aged 20–45 years. Approximately, 1% of females experience recurrent miscarriage.[3]

Uterine fibroids are the most common benign tumours of the smooth muscle within the female genital tract, affecting 20–40% of females during their reproductive years. They are frequently encountered in patients who are undergoing fertility treatment.[4] Intracavitary fibroids occur in approximately 5–18% of infertile patients and in about 7% of patients with unexplained infertility.[5,6] Endometrial polyps, which are growths within lining of the uterus are also prevalent, were found in an estimated 11–45% of patients undergoing IVF and in 15–25% of those with unexplained infertility.[5,7,8]

Some evidence, primarily from observational studies, suggests that submucous fibroids may negatively affect reproductive performance.[9] They can distort the endometrial cavity and potentially disrupt subendometrial blood flow.[10] Similarly, endometrial polyps may impair fertility, as indicated by their negative effect on markers of endometrial receptivity such as HOXA10 and HOXA11 messenger ribonucleic acid levels.[7]

Surgical removal of submucous fibroids to improve reproductive outcomes has become widely accepted,[11] despite the lack of high-quality randomised controlled trials (RCTs) supporting this practice, and most evidence are from small observational studies.[11,12] Similarly, hysteroscopic removal of endometrial polyps has gained popularity in treating patients with fertility issues, although robust evidence from RCTs is lacking.[13] Most studies examining the effect of endometrial polyps on pregnancy rates are small, observational and non-controlled,[13–21] with conflicting

results regarding their impact on conception rates. A 2010 systematic review highlighted the suboptimal quality and contradictory nature of the available evidence.[22] A meta-analysis demonstrated an increase in clinical pregnancy rates after hysteroscopic resection of fibroids after intrauterine insemination (IUI) but not after IVF; the authors highlighted the need for more RCTs.[23]

Despite National Institute for Health and Care Excellence (NICE) guidance stating that the effectiveness of surgical resection has not been established,[24] hysteroscopic removal of submucous fibroids and endometrial polyps is routinely performed for patients with infertility, including those with unexplained infertility and recurrent miscarriage. This practice carries significant costs and risks, some of which may further impair fertility.[11,25] Complications such as uterine perforation, Asherman syndrome and intrauterine adhesions may adversely affect fertility.[26,27] Furthermore, these surgical procedures place a significant economic burden on healthcare systems and can cause patients considerable anxiety, affecting pain perception and satisfaction.[28]

### *Aims and objectives*

The overall aim of HELP Fertility? was to examine the clinical and cost-effectiveness of hysteroscopic removal of submucosal fibroids and endometrial polyps, compared to no hysteroscopic removal, in patients presenting with infertility and recurrent miscarriage.

The main trial included two RCT internal pilots, with the objective of assessing the feasibility of conducting two multicentre RCTs: one for participant with endometrial polyps, and one for participant with submucous fibroids.

The objectives of the main trial were to:

1. determine the clinical and cost-effectiveness of the hysteroscopic removal of endometrial polyps, compared to no hysteroscopic removal, to improve fertility in participants who are suffering from infertility or recurrent miscarriage
2. determine the clinical and cost-effectiveness of the hysteroscopic removal of submucous fibroids, compared to no hysteroscopic removal, to improve fertility in participants who are suffering from infertility or recurrent miscarriage
3. determine participant experience and satisfaction and procedure-related complications
4. assess the long-term effect of hysteroscopic resection of endometrial polyps and submucous fibroids by collecting and analysing routinely collected NHS data.

## Methods

The trial was designed as an 'Umbrella' RCT,[29] with two concurrent pragmatic, parallel group, open, multicentre RCTs, with the aim of establishing the superiority of hysteroscopic removal of submucous fibroids/endometrial polyps compared to no hysteroscopic removal. Methods for each RCT were the same except where they are described here separately. Not all planned analyses were undertaken due to the early closure of the trial.

Randomised controlled trial 1: Submucous fibroid population: participants with a history of infertility or recurrent miscarriage and trying to conceive naturally or with fertility treatment and who meet the inclusion criteria.

Randomised controlled trial 2: Endometrial polyp population: participants with a history of infertility or recurrent miscarriage and trying to conceive naturally or with fertility treatment and who meet the inclusion criteria.

### *Sample size*

The primary outcome for both trials was the LBR defined by the number of live births after 24 weeks of gestation within the 15-month post-randomisation follow-up period relative to the number of women randomised. Assuming a 10% LBR in the no hysteroscopic removal (control) group and 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, required 266 women per group (532 in total). Adjusting for a predicted attrition rate of 5%, we required 560 participants to be randomised. A similar sample size was required for RCT2 (polyp population), that is 560 participants, so a total of 1120 participants were required for RCT1 and RCT2 combined.

### *Nine-month pilot*

The trials commenced with a 9-month internal pilot phase to determine whether the recruitment strategy and site set-up were feasible, whether intervention arm participants received resection within an acceptable time frame (set at 3 months post randomisation), and finally, whether the level of withdrawal (crossover) from the control treatment (the number of participants in the control arm who undergo resection) was acceptable. The pilot study used the same trial procedures as later described for the main trial. The recommendations of Avery *et al*. were used to set green/amber/red criteria for the pilot phase of both RCTs (see *Table 2* in *Results summary*).[30] Criteria were set prior to the COVID-19

pandemic in which fulfilment of the 'green' criteria would indicate continuation of the trial, fulfilment of the 'amber' criteria would indicate that steps would be taken to regain ground and fulfilment of the red criteria would indicate the trial was not feasible.

### *Identification and recruitment*

Participants were recruited from centres across the UK, including secondary and tertiary fertility or gynaecology units providing care for patients with infertility and recurrent miscarriage. Participants were eligible to take part if they met the following inclusion criteria:

1. History of primary or secondary infertility (defined as a patient 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 patient seeking fertility treatment who is using artificial insemination to conceive (with either partner or donor sperm) if they have not conceived after six 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 of gestation).

2. Diagnosed endometrial polyps or submucosal fibroids that are ≤ 3 cm in size or in cases where multiple fibroids and or polyps are present, these amass to ≤ 3 cm in total.

The following exclusion criteria were 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 syndrome.
3. Malignancy of endometrial polyp/submucous fibroid is suspected.
4. The patient was taking part in any other interventional infertility/fertility trial.
5. Pregnancy, or pregnancy is suspected.
6. Previously randomised into the other HELP Fertility? trial (RCT1 or RCT2).

Participants were identified either as incident cases, as they attended a fertility or recurrent miscarriage clinic and the presence of polyps or fibroids were confirmed, or via review of medical notes to identify those patients who have had polyps or fibroids diagnosed but not resected. Participants underwent assessments to confirm eligibility by using the sites' usual procedures to diagnose and confirm measurement of polyps and/or fibroids (*Table 1*).

### *Randomisation*

The main trial aimed to recruit 560 participants in each RCT across the UK, with a recruitment duration of 30 months. Eligible participants were randomised to receive either hysteroscopic resection of the abnormalities (intervention group) or no hysteroscopic resection (control group). Randomisation was done using a centralised web-based randomisation system (SCRAM) hosted by Sheffield Clinical Trials Research Unit (CTRU). Participants were allocated on a ratio of 1 : 1 to either the intervention or control group. Stratified block randomisation was used, stratified by (1) recruiting centre and (2) infertility or recurrent miscarriage. A trial statistician generated the allocation sequence using the SCRAM system. Research

**TABLE 1** Eligibility screening methods

| Method | A – used as a diagnosis technique | B – used as a measurement technique |
|---|---|---|
| Hysteroscopy | Yes | No |
| 2D ultrasound | Yes | Yes |
| 3D ultrasound | Yes | Yes |
| CT/MRI scan | Yes | Yes |
| Hysterosalpingography | Yes | Yes |
| HyCoSy | Yes | Yes |
| Saline sonography | Yes | No |

CT, computerised tomography; HyCoSy, hysterosalpingo contrast sonography; MRI, magnetic resonance imaging.

staff at recruiting centres were unable to access the randomisation sequence. Following randomisation, the participant was informed of their allocation, and a record of this was entered into the participant's medical notes, with the next steps in treatment arranged. If sites had the capacity to facilitate randomisation during an investigative hysteroscopy, participants were consented prior to, and were randomised during the procedure, if found eligible. Participants randomised to the intervention arm received resection during the same procedure.

### Blinding

The Trial Steering Committee (TSC), the study statisticians and health economists were blinded to treatment allocation while the trial was ongoing. Neither participants nor clinicians were not blinded to treatment allocation due to the surgical nature of the intervention.

### Treatment allocation

Originally, it was planned that participants randomised to the intervention arm would be scheduled for resection within the 18-week patient pathway, but due to the pandemic, it was agreed that this should be scheduled within the sites' own guidelines. As hysteroscopic resection is a routine surgical procedure, a pragmatic approach was taken, which allowed centres to use their own local hysteroscopic techniques, which were conducted in line with the World Health Organization checklist prior to resection.[31] Sites were informed to commence with other expected fertility treatments as soon as possible following hysteroscopic resection.

Participants randomised to the control group did not receive hysteroscopic resection, and sites were informed to commence other expected fertility treatments as soon as possible following randomisation.

Compliance was measured by the staff member recording whether the participant attended the clinic and received the procedure per protocol (PP). If fibroids/polyps were found to be misdiagnosed when carrying out the hysteroscopic procedure, and were confirmed by histology result, the participant was to remain in the originally assigned RCT and was to be followed up, with their data and outcomes to be analysed as part of the 'intention-to-treat' (ITT) analysis.

### Follow-up

Participants were followed up to 15 months post randomisation. If participants reached 24 months post randomisation before the study closed, a follow-up assessment was carried out at this time point.

### Outcomes

The primary outcome was LBR. The unit used to compare between arms is the proportion of participants who gave birth to one or more live infants, after 24 weeks gestation, before their 15-month post-randomisation follow-up contact or notes review. A participant contributed (one) to the numerator if they give birth to one or more live infants. Otherwise, participants did not contribute to the numerator.

The following secondary clinical outcomes were collected:

1. Live birth within 24 months of randomisation.
2. Time from randomisation to live birth.
3. Time from randomisation to clinical pregnancy.
4. Clinical pregnancy (an observation of viable intrauterine pregnancy with a positive heart pulsation seen on ultrasound at/after 8 weeks of 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); still birth (delivery of a still born fetus showing no signs of life after 24 weeks of gestation); and ectopic pregnancy rates (pregnancy outside the normal uterine cavity).
5. Details 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).
6. Details of fertility treatments received, including details of medications received and assisted reproductive techniques received.
7. 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 were collected regarding any false diagnoses of endometrial polyps/submucous fibroids.
8. Number of participants in the control arm who undergo resection.
9. COVID-19 vaccination status (first, second, booster, approximate date and type of vaccine). Note: this outcome was added in response to the pandemic to assess any impact of vaccine on pregnancy outcome.
10. Adverse events due to procedure-related and gynaecological/obstetric-related complications.
11. Patient satisfaction, using a questionnaire designed with patient and public involvement (PPI) to assess

general patient satisfaction with the hysteroscopic resection procedure (intervention arm only participants).
12. Health resource use of the participant measured at baseline, 6, 15 and 24 months post randomisation.
13. Participant costs measured following hysteroscopy for participants randomised to hysteroscopic resection.
14. Cost per live birth gained.

### *Changes to initial trial design*

The original trial design is presented in *Figure 1*. The study planned to follow up participants at 6, 15, 24 months and up to 7.5 years in a long-term study (calculated from first participant enrolled in the trial). The long-term follow-up study would have used data available in medical notes and/or routine NHS data to collect pregnancy outcomes, fertility treatments and resections. However, due to the trial's early closure, sites were informed to follow up all 35 participants to 15 months; 24-month data were also collected for participants who had reached this time point before the 15-month data collection visit of the last participant recruited.

#### Removal of the permitted crossover

The original pre-COVID trial design involved a 'protocolised' permitted crossover for participants allocated to the control arm. This meant that control participants were offered the opportunity to 'crossover' and receive removal of fibroids/polyps at or beyond 6 months post randomisation. The minimum 6-month time frame was chosen as this would not have impacted the primary outcome, as all live births at 15 months should result from the intervention arm. The crossover was included in the original trial design as it was anticipated that some participants in the control arm would want to receive the intervention if they had not already conceived plus, clinicians highlighted that the study required a cultural change in practice.

It was later recognised that the crossover offer could confuse the position of equipoise, giving potential participants the impression that removal of fibroids/polyps would have a positive effect on infertility, which could impact recruitment negatively. In addition, the COVID pandemic created unpredictable and variable surgery wait times. With no assurance that surgery in the intervention arm could be scheduled within 6 months, it was increasingly likely that the primary outcome would be confounded.

Following discussion with the PPI panel, the 'protocolised' offer to crossover was removed from the trial design. Control participants could still, however, request to have the procedure if they wished, if this was available to them locally – effectively withdrawing from their allocated trial arm.

### *Cost-effectiveness methods*

The primary objective of the economic analysis was to estimate the cost per extra live birth associated with hysteroscopic removal of endometrial polyps and submucosal fibroids versus no surgical intervention at 15 months. The primary analysis was planned to take the NHS and Personal Social Services (PSS) perspective as recommended by NICE, and the analyses were planned to be undertaken separately for each of the RCTs included in the study.[32] Costs to be included in the analyses were those associated with hysteroscopic resection, hospitalisations associated with adverse events due to surgery, NHS-funded fertility treatments and other primary and secondary care and prescribed medication costs related to the fertility journey. Patient-centred costs related to time taken to travel to appointments to receive the intervention (and the loss of productivity associated with attending such appointments), as well as non-NHS funded fertility treatments, were planned to be included in a secondary analysis taking a societal perspective. Resource use questionnaires were designed to collect resource use data.

Two sets of economic analyses were planned – a primary analysis based on an ITT analysis of the trial data and a supplementary analysis based on analyses that adjust for potentially informative withdrawal of randomised treatment or trial withdrawal. The primary economic analysis was planned to include a 15-month time horizon based on the primary outcome of the trial (LBR at 15 months). A secondary analysis was planned to include a 24-month time horizon, in line with a secondary statistical analysis of the LBR outcome – LBR at 24 months.

As a result of the early closure of the study, the economic analysis was substantially reduced. Instead of separate analyses for the submucous fibroid and endometrial polyp populations, one analysis was conducted, merging the two populations. In addition, analyses were only undertaken adopting an NHS and PSS perspective and were only undertaken for a time horizon of 15 months.

Details associated with hysteroscopic resection were recorded in case report forms (CRFs), which included information on whether the intervention was carried out as an inpatient, outpatient or as a day case, as well as information on length of stay and preoperative and postoperative appointments. These were costed using appropriate Healthcare Resource Groups and national unit

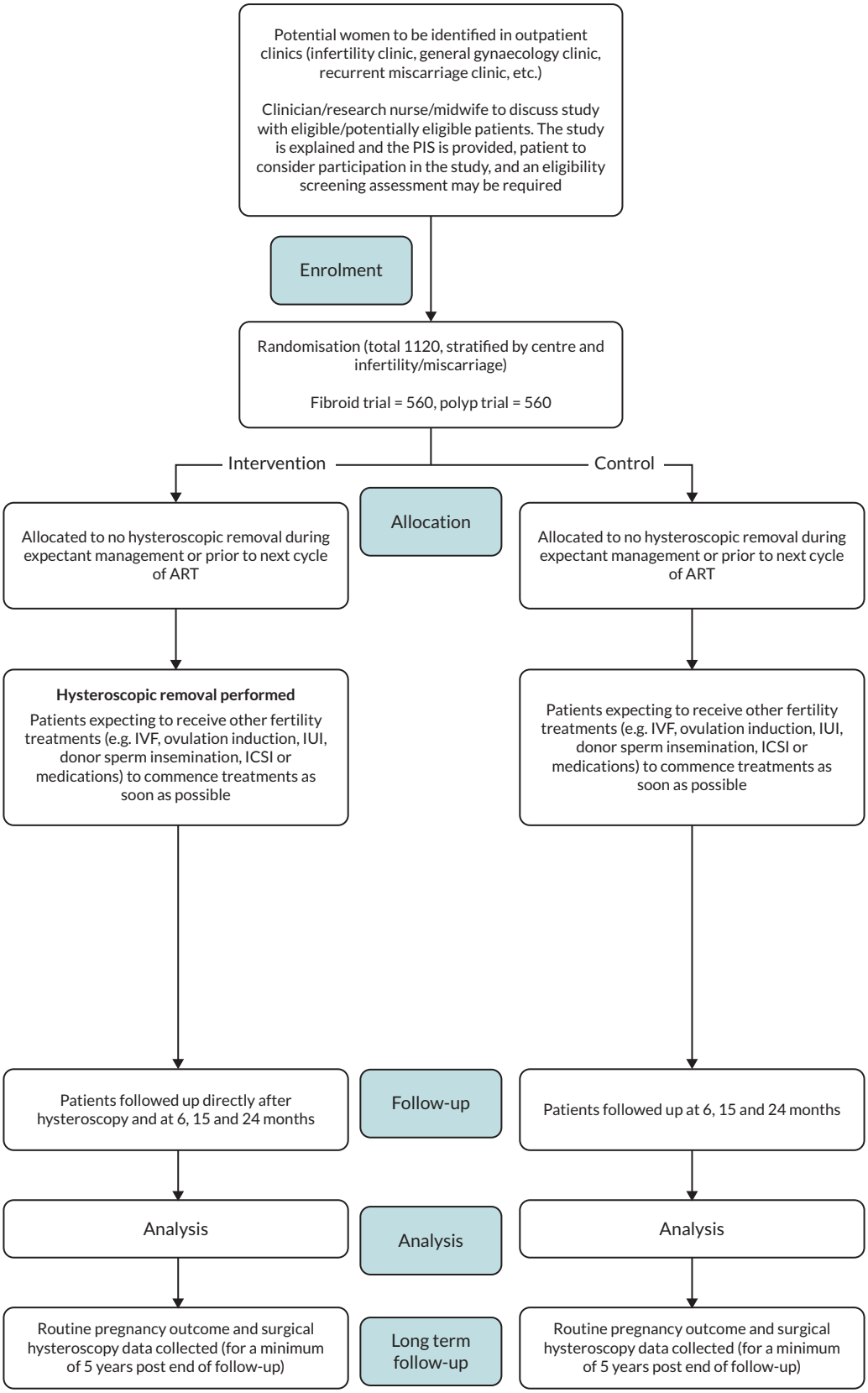


**FIGURE 1** The HELP Fertility? RCTs flow diagram. ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; PIS, patient information sheet.

costs, pertaining to the year 2022–3.[33,34] Resource use questionnaires were used to record information on the NHS and PSS resource use that was not related to the hysteroscopic resection (since this was collected in the CRFs) but was related to the fertility journey. Due to the reduced scope of the economic evaluation after the early closure of the study, medication costs reported in the resource use questionnaires were not included in our analysis. However, costs associated with primary and secondary care and NHS-funded fertility treatments were included.

The resource use questionnaire was administered at the 6- and 15-month time points, and participants were asked to report their resource use for the last 3 months. Therefore, costs estimated based on questionnaires collected at 6 months were multiplied by two to obtain costs for the first 6 months of the study period, and costs estimated based on questionnaires collected at 15 months were multiplied by three to obtain costs from months 7 to 15. Unit costs used are presented in *Appendix 1*, *Table 10*. Discounting was not applied due to the short time horizon analysed.

To allow for an easier interpretation, results are reported with respect to live births per 1000 women treated. The incremental cost-effectiveness ratio (ICER) was calculated as the incremental cost per extra live birth per 1000 women treated for those randomised to hysteroscopic resection compared to those randomised to no resection. Bootstrapping, a resampling method, was used to obtain 95% bias-corrected confidence intervals (CIs) to show the uncertainty around the ICER, using 5000 simulations. The primary analysis used the full ITT sample, and a secondary analysis consisted of participants with complete data at the baseline, 6- and 15-month time points (referred to as a 'complete-case' analysis). Results are presented graphically using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

## Results summary

No papers have been submitted for the HELP Fertility? trial to date.

### *Nine-month internal pilot*

*Table 2* summarises progress of the internal pilot against the pre-COVID-19 set progression criteria.

Leading site, Sheffield Teaching Hospitals (STH), was opened with a 4-month delay due to the COVID-19 pandemic, with significant further delays to the opening of subsequent sites. It was agreed with the NIHR that the internal pilot would commence formally upon recruitment of the first participant at a non-STH site. At 9 months post this point, 14 sites were open, of which 9 had recruited a first participant. Approvals were pending at a 15th site and were in progress at a further 13 sites. Some sites had required up to 6 months to recruit their first participant.

During the pilot, 29 participants were recruited, with recruitment rates (participant per site per month) lower

**TABLE 2** Trial progress summary against progression criteria

| | Domain | Target at 9 months | Green | Amber | Red | Status | |
|---|---|---|---|---|---|---|---|
| 1 | Sites open with one participant randomised | 30 | 25+ | 15–24 | < 15 | 14 sites open (9 have recruited)<br>1 site – R&D approval pending<br>13 further sites were being supported to progress with providing approval | |
| 2 | Participant recruitment | Fibroids<br>0.67 per site per month | Min 80% (0.5) | 60–80% (0.4) | < 60% | Actual 0.16 | Adjusted 0.23 |
| | | Polyps<br>1.3 per site per month | Min 40% (0.5) | 30–40% (0.4) | < 30% | Actual 0.27 | Adjusted 0.39 |
| 3 | Intervention participants having resection within 3 months post randomisation | 100% | 80% | < 80% | Not applicable | 90% | |
| 4 | Withdrawal from control treatment (resection within 6 months post randomisation) | 0% | < 10% | 10–50% | > 50% | Zero for participants who have reached the 6 months post randomisation time point | |

R&D, research and development.

than the pre-pandemic set targets. The 'actual' calculated recruitment rates include the months in which sites were open, but were inactive or had limited research activity due to COVID, reduced staffing levels or a delay in resuming their hysteroscopy service.

Upon recommendation of the Data Monitoring and Ethics Committee, an adjustment was made to remove the number of inactive months *before* first participant was recruited at each site. The adjusted rates did not, however, allow for months of *reduced* site activity, post first participant recruitment, as this was difficult to quantify. The adjusted recruitment rate for the Fibroid trial was 0.23 participants/site/month, while for the Polyp trial, this was 0.39 participants/site/month, measured against a 'green' recruitment target = 0.5 and 'amber' recruitment target = 0.4 participants/site/month.

Ninety per cent of participants allocated to have hysteroscopic resection of their fibroid(s) or polyp(s) underwent surgery within 3 months of being randomised, exceeding the progression criteria of 80%.

No participants had withdrawn from the control treatment arm by the 9-month pilot reporting date.

## *Main trial*

### Recruitment, demographics and baseline characteristics

The recruitment flowchart is presented in *Appendix 1*, *Figure 5*. From April 2021 to March 2023, the trial opened in 16 NHS sites, with 39 participants consenting to take part, of which 35 were randomised. Thirty-three were diagnosed with infertility, and 2 with recurrent miscarriage. Sixteen participants were randomised to control, and 19 participants were randomised to the intervention arm. The primary outcome was completed by 34 participants; 24-month data were collected for 14 participants who reached this time point before the 15-month data collection visit for the last participant recruited (6 control participants and 8 intervention participants). Demographics and baseline characteristics are presented in *Appendix 1*, *Table 11*.

### Primary outcome, primary analysis: participants experiencing a live birth within 15 months of randomisation, intention to treat

Within the ITT analysis population, treatment assignment is defined by the participant's randomisation allocation regardless of what happens after randomisation.

The primary study outcome measure was the proportion of participants who experienced any live birth by the time of their 15 months post-randomisation follow-up contact or notes review. The comparison between arms was undertaken using an ITT analysis and with no adjustment for baseline (nor subsequent) characteristics.

The proportions with a live birth were 18.8% (3/16) in the control arm (no resection) and 15.8% (3/19) in the intervention arm (hysteroscopic resection).

The comparisons are presented in *Table 3* using a range of statistics: absolute risk difference, relative risk and odds ratio (OR). The reference case, for relative risk and OR, was the control (no resection) arm; 95% CIs are provided for each comparison statistic. In our sample of 35 participants, we observed a higher LBR in the control (no resection) group compared to the intervention (hysteroscopic resection) group at 15 months post randomisation. However, because of the small sample size, the CIs for the estimated treatment effects were wide and were consistent with no effect or difference in the birth rate between the groups in the population.

**TABLE 3** Primary outcome, number and proportion of randomised participants who experienced a live birth within 15 months of randomisation primary analysis (ITT population)

| Outcome | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | RD[a] (95% CI) | RR (95% CI) | OR (95% CI) |
|---|---|---|---|---|---|
| Participants who experienced a live birth within 15 months | 3 (18.8) | 3 (15.8%) | −3.0% (−31.1% to 25.2%) | 0.84 (0.20 to 3.61) | 0.81 (0.14 to 4.72) |

RD, risk difference; RR, relative risk/risk ratio.
a (Absolute) RD (difference in percentage of participants who experienced a live birth within 15 months).

**Note**
Control (no resection) is the reference group.

### Secondary clinical outcome analyses

The PP analysis population is a subset of the ITT analysis population who additionally complied with the protocol requirements. As with the ITT analysis population, treatment assignment is defined by the participant's randomisation allocation.

The primary study outcome measure was compared using a PP analysis with no adjustment for baseline (nor subsequent) characteristics. The ITT and PP populations were comparable, and the analysis yielded unsurprisingly similar results (see *Appendix 1*, *Table 12*). Results after adjustment for the randomisation stratification factors were also comparable (see *Appendix 1*, *Table 13*).

Time-to-event analyses were undertaken from randomisation to (1) first live birth and (2) first clinical pregnancy, for both the ITT and PP populations. The hazard ratios are presented in *Appendix 1*, *Table 14*. Kaplan–Meier plots for these data are presented in *Appendix 1*, *Figure 6*.

Cox proportional hazards regression analysis was used to estimate the hazard ratio for participants in the intervention (hysteroscopic resection) arm, experiencing a clinical pregnancy and – separately – a live birth, compared to the participants in the control (no resection) arm. Models were estimated using all earliest clinical pregnancy (11, 5 in the intervention arm and 6 in the control arm) and live birth (10, 4 in the intervention arm and 6 in the control arm) outcomes recorded during the trial, both for the ITT population and the PP population. No covariates, other than treatment arm, were included.

The estimates from the Cox models provide no evidence of a statistically significant (at the 95% confidence level) difference in the hazard of participants in the intervention (hysteroscopic resection) arm compared to those in the control (no resection) arm for experiencing a clinical pregnancy or live birth using either the ITT population or the PP population.

### Other secondary clinical outcome measures

No pregnancy outcomes other than *live birth* were reported in the study for any identified *clinical pregnancies*.

*Miscarriage* (including PUL) was recorded as an outcome of some pregnancies at, or before, the time of some participant's 8-week scan(s).

*Live birth*, *clinical pregnancy and miscarriage* are reported for the ITT population (*Table 4*). Note that not all participants reached and completed the 24-month data collection time point.

*Miscarriage* is additionally reported for the subset of the ITT population who experienced a pregnancy before their 15-month post-randomisation follow-up contact or notes review (*Table 5*).

### Safety

No serious adverse events were recorded in the course of the study. A single (1) adverse event was recorded in the trial in the control (no resection) safety population: postpartum haemorrhage.

### Patient satisfaction

A questionnaire was sent to all participants allocated to the intervention. Summary statistics were calculated on the mean level of satisfaction, tolerability and impact of the procedure (*Table 6*).

**TABLE 4** Other secondary clinical outcomes, ITT population

| Participants who experienced a | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) |
|---|---|---|
| Live birth within 24 months | 5 (31.2%) | 3 (15.8%) |
| Clinical pregnancy within 15 months | 6 (37.5%) | 5 (26.3%) |
| Miscarriage within 15 months | 3 (18.8%) | 1 (5.3%) |

**TABLE 5** Outcome of miscarriage among the subset of the ITT population who experienced a pregnancy

| Participants who experienced a | Control (no resection) (*n* = 9) | Intervention (hysteroscopic resection) (*n* = 5) |
|---|---|---|
| Miscarriage within 15 months | 3 (33.3%) | 1 (20.0%) |

**TABLE 6** Patient satisfaction with hysteroscopic resection procedure

| Patient satisfaction measure | Mean value (responses) |
|---|---|
| General satisfaction (1–5)[a] | 4.4 (17) |
| Tolerability of procedure (1–3)[b] | 2.4 (17) |
| Negative impact of procedure on usual activities (1–3)[c] | 2.2 (17) |

a One being very dissatisfied, and five being very satisfied.
b One being not tolerable, and three being very tolerable.
c One being unaffected, and three being unable.

## Clinical treatment

The number and proportion of participants in the intervention (hysteroscopic resection) arm who received hysteroscopic resection within the 3 months (91 days) following randomisation were 16 (84.2%).

The following data are presented in *Appendix 1*, *Tables 15–22*.

- Details of hysteroscopic resection procedure(s) received by all participants who received hysteroscopic resection (in both, intervention and control, arms).
- Details of the locations of endometrial polyps or submucous fibroids among all participants who received hysteroscopic resection (in both, intervention and control, arms).
- Details of the methods used to diagnose and accurately measure endometrial polyps or submucous fibroids among all randomised participants.
- Details of the characteristics of the fertility treatments initiated by the date of participants' 6-month post-randomisation follow-up contacts (or notes reviews).
- Detail of fertility treatments initiated after the 6-month post-randomisation follow-up contacts and by the date of the 15-month post-randomisation follow-up contacts.
- Characteristics of all embryos transferred in the course of fertility treatments prior to participants' 6-month post-randomisation follow-up contacts and between 6- and 15-month follow-up contacts.
- COVID-19 vaccination status of all randomised participants.

### *Cost-effectiveness results*

This section reports results from the cost-effectiveness analysis in line with the Consolidated Health Economic Evaluation Reporting Standards guidance.[35] Thirty-three (94.3%), 27 (77.1%) and 24 (68.6%) participants completed the resource use questionnaire at baseline, 6 months and 15 months, respectively.

## Costs and resource use

The main costs incurred during the study period were related to hysteroscopic resection. In the 15-month study period, 18 participants in the intervention group underwent a hysteroscopy, and 2 of them had an additional hysteroscopy. Four participants randomised to the control group underwent a hysteroscopy. During the 15-month study period, 14 (87%) participants randomised to the control group and 12 (63%) participants randomised to hysteroscopic resection underwent fertility treatment. A summary of estimated costs incurred during the 15-month study period is provided in *Table 7*. Sample means are presented along with bias-corrected bootstrapped 95% CIs. It is notable that costs associated with midwife visits were higher in the control group (although this is not statistically significant), which is likely to be due to the larger number of live births in this group. The point estimate for 'Other NHS resource use' costs was much higher in the intervention group – this is primarily due to a single patient undergoing oocyte recovery with intracytoplasmic sperm injection (ICSI), which is a costly procedure.

Resource use in the 3-month period prior to baseline was also analysed. There were no statistically significant differences between treatment groups [£613 (95% CI £219 to £1201) in the control group; £540 (95% CI £180 to £1149) in the intervention group].

## Cost-effectiveness analysis

*Table 8* presents the main results of the cost-effectiveness analysis. Sample means are presented for total costs and LBRs per 1000 women treated along with bias-corrected bootstrapped 95% CIs.

In the ITT analyses, the mean costs were £5652 in the hysteroscopic resection group compared with £2953 in the control group (mean difference £2699, 95% CI −£42 to £5695). For every 1000 women treated, the intervention would result in 30 fewer live births than the control group – though the 95% CIs around this figure are wide, ranging from 270 fewer live births to 234 additional live births.

**TABLE 7** Summary of mean costs

| Resource use | Cost, mean (bias-corrected bootstrapped 95% CI) | |
|---|---|---|
| | Control (no resection, *n* = 16) | Intervention (hysteroscopic resection, *n* = 19) |
| Hysteroscopy | £341 (£5 to £140) | £1811 (£1225 to £2511) |
| Delivery of baby | £595 (£168 to £1466) | £579 (£141 to £1454) |
| GP | £72 (£18 to £156) | £136 (£32 to £291) |
| Practice nurse | £12 (£2 to £32) | £7 (£0 to £16) |
| Dentist | £0 | £9 (£0 to £17) |
| Pharmacist | £6 (£0 to £17) | £14 (£2 to £31) |
| Dietitian | £21 (£0 to £104) | £0 |
| Health visitor | £20 (£0 to £39) | £164 (£0 to £329) |
| Midwife | £504 (£125 to £1068) | £188 (£30 to £543) |
| Planned hospital visits | £912 (£183 to £2269) | £643 (£231 to £1209) |
| Accident and emergency | £22 (£0 to £45) | £0 |
| Preoperation visits | £13 (£0 to £66) | £123 (£78 to £201) |
| Follow-up visits | £372 (£305 to £398) | £933 (£302 to £2625) |
| Other NHS resource use | £63 (£0 to £316) | £1047 (£28 to £3909) |
| **Total mean costs** | **£2953 (£1662 to £4592)** | **£5652 (£3573 to £8501)** |

GP, general practitioner.

**TABLE 8** Incremental cost-effectiveness analysis means with bias-corrected 95% CIs

| Analysis type | Control | Intervention (hysteroscopic resection) | Incremental difference (intervention – control) | ICER |
|---|---|---|---|---|
| ***Analysis of ITT population*** | | | | |
| Total costs per patient | £2953 (£1662 to £4592) | £5652 (£3573 to £8501) | £2699 (£42 to £5695) | −£91 (interpretation: additional £91,000 cost per one live birth lost in 1000 treated women) |
| LBR per 1000 treated | 188 (63 to 500) | 158 (53 to 421) | −30 (−270 to 234) | |
| ***Analysis of complete case population*** | | | | |
| Total costs per patient | £3960 (£2113 to £6117) | £7920 (£5141 to £11,665) | £3960 (£258 to £7720) | −£79 (interpretation: additional £79,000 cost per one live birth lost in 1000 treated women) |
| LBR per 1000 treated | 300 (16 to 584) | 250 (83 to 667) | −50 (−433 to 317) | |

At the mean, hysteroscopic resection resulted in fewer live births, but increased costs, resulting in a negative ICER of −£91 and implying that hysteroscopic resection is not cost-effective compared to the control treatment. However, due to the small sample size, these results are extremely uncertain and should be interpreted with care. CIs for incremental costs and the incremental LBR spanned zero – indicating that there is a small chance that the intervention could be cost saving and a chance that the intervention could increase the LBR.

*Figure 2* presents the cost-effectiveness plane for the ITT analysis; 56% of the bootstrap samples resulted in the control treatment representing a 'dominant' strategy in economic terms – whereby the control group has a higher LBR and lower costs. In 0.05% of samples, hysteroscopic resection was dominant. In 41% of samples, hysteroscopic resection was more expensive than the control group and resulted in a higher LBR, and in the remaining 2% of samples, the intervention was less costly than the control but also less effective.

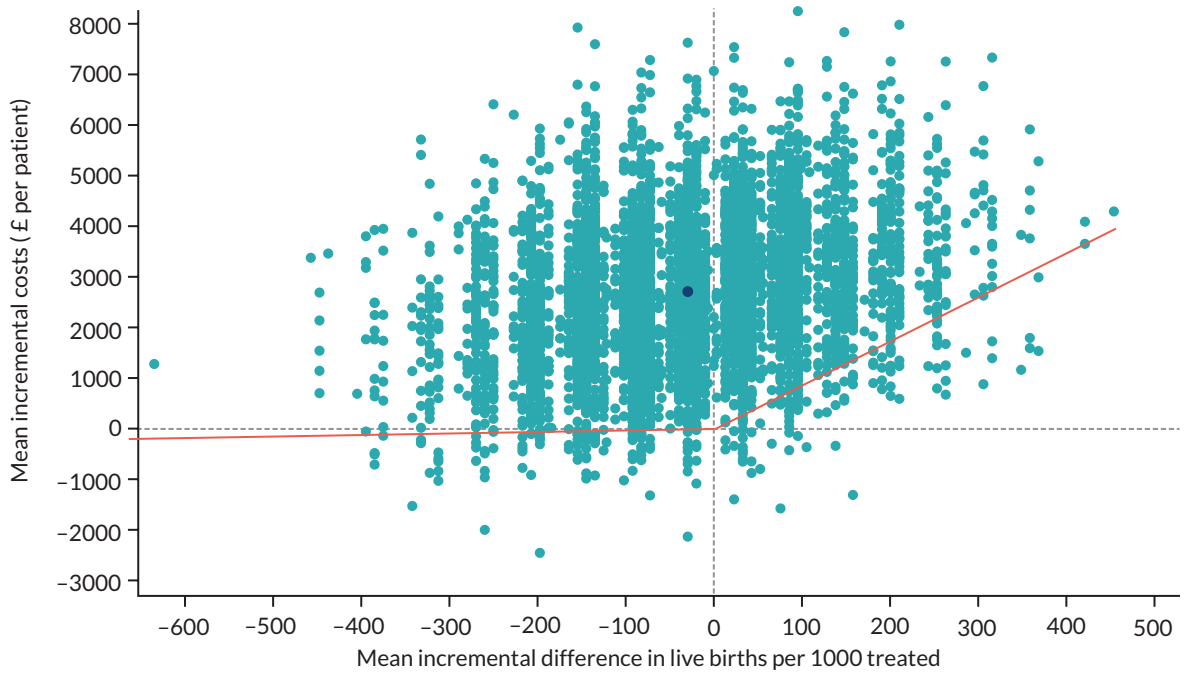


**FIGURE 2** Cost-effectiveness plane: incremental difference in costs and live births between the hysteroscopy group and the control group (5000 bootstrap replicates) – ITT analysis.

Considerable care must be taken when deriving CIs for ICERs when bootstrap samples lie in multiple quadrants of the cost-effectiveness plane.[36,37] If bootstrap samples fall within all four quadrants, replicates cannot simply be ordered by size of the ICER and centiles taken, because the interpretation of negative ICERs depends on the quadrant that the sample falls in. In *Figure 2*, we have indicated the region of the plot that contains 95% of the bootstrap samples by using two red lines beginning at the origin of the graph. Bootstrap samples that lie above these lines fall within the 95% CI. However, the cost-effectiveness ratios that the two lines represent are both positive – the line in the north-east quadrant represents a positive ICER value, and the line in the south-west quadrant also represents a positive ICER value. Yet, the 95% region also includes all bootstrap samples that fell within the north-west quadrant – which represent negative ICERs. Therefore, in this instance, a valid 95% CI for the ICER cannot be reported.

Instead, CEACs can be used to report the probability that the intervention represents a cost-effective use of NHS resources. *Figure 3* presents the CEAC for the ITT analysis. At a cost-effectiveness threshold of £20,000 per additional live birth, there is a 10% probability that hysteroscopic resection represents the most cost-effective intervention and a 90% probability that the control group is most cost-effective. The probability of hysteroscopic resection representing the most cost-effective intervention increases to 40% at a cost-effectiveness threshold of £200,000 per additional live birth. This probability never rises above 44%, because the intervention was dominated by the control group in 56% of the bootstrap samples. Because there is a 3% probability that hysteroscopic resection is cost saving, compared to the control group, there is a 3% probability that the intervention is cost-effective even with a threshold willingness to pay of £0 per additional live birth.

Results from the complete case analysis were very similar to those from the ITT analysis, with plots being presented in *Appendix 2*, *Figures 7* and *8*.

## Discussion/interpretation

### *Principal findings*

In a limited group of 35 participants, the birth rates at 15 months in both the control 'no resection' group and in the intervention 'hysteroscopic resection' group were similar. A greater proportion of participants (3 in 16) in the 'no resection' group experienced a miscarriage (before ascertainment of clinical pregnancy) compared to those in the group receiving hysteroscopic resection (1 in 19). The numbers recruited into this study are small and so no strong clinical interpretation can be reached through the statistical analysis.

The 24-month data were acquired for only 14 participants in the ITT population, and it is not possible to draw any conclusions from this data.

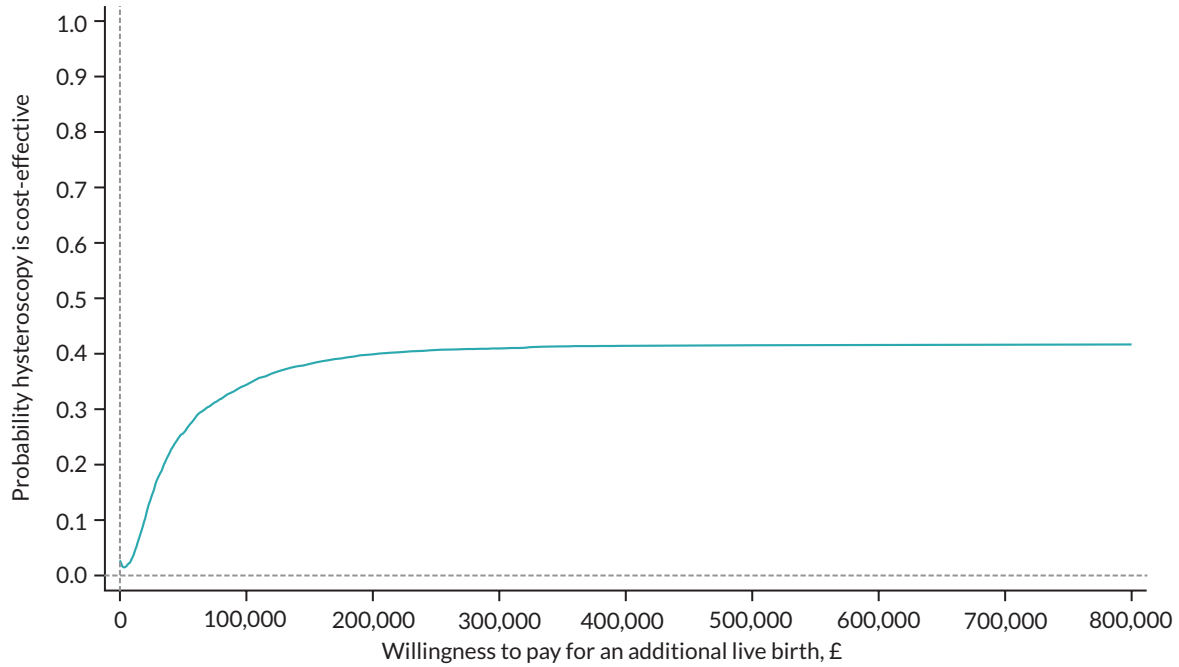


**FIGURE 3** Probability that hysteroscopy is cost-effective compared to the control treatment – ITT analysis.

There were no statistically significant differences in costs, or in the LBR, between randomised groups in the HELP Fertility? RCT. However, point estimates of the sample means indicate higher costs in the hysteroscopic resection group and a marginally lower LBR than the control treatment. Higher costs are driven by the costs associated with receiving hysteroscopy, and this did not appear to result in an increase in the LBR. However, it is crucial to emphasise that these results are extremely uncertain. Our analyses suggest that there is a 10% probability that hysteroscopic resection represents the most cost-effective intervention at a willingness to pay per additional live birth of £20,000, and this rises to 40% at a willingness to pay per additional live birth of £200,000. However, even at unlimited levels of willingness to pay, this probability never increases above 44%, because, based on the trial data, we estimate that there is a 56% probability that the control treatment results in a higher LBR than hysteroscopic resection.

## *Reflections and challenges*

### Participant and clinical equipoise

Resection of uterine abnormalities has been routine practice in the NHS for many years and participant and clinician equipoise was identified as a potential challenge in the grant application. We built a research team of clinical co-applicants from a range of gynaecology and fertility units across the UK and carefully developed balanced participant-facing materials (e.g. information sheets and an animated recruitment video) with a Patient, Public Involvement and Engagement panel. Of the 68 consenting participants, 11 discontinued prior to randomisation stating they did not want to be randomised to the control arm, while 4 stated they did not wish to be randomised to receive the intervention (see *Appendix 1*, *Figure 5*). We found that with good communication, participants were able to make an informed decision and were more receptive to taking part in the trial. Some participants, in fact, were keen to use the randomisation system to make the decision about surgery on their behalf.

Clinical equipoise was a barrier at some recruiting sites, with some consultants unwilling to offer the trial to patients. This was also a barrier to opening the trial within some NHS Trusts.

During the COVID-19 pandemic, few patients were seen at point of diagnosis of fibroids/polyps, meaning many patients approached were already on the waiting list for surgery. We found that approaching patients at the point of diagnosis reduced the patient equipoise barrier, helping participant recruitment. As post-pandemic surgery wait times decreased, we intended to increase patient approach at the point of diagnosis.

### Site set-up and recruitment

The research team faced considerable obstacles in setting up study sites and enrolling participants, primarily as a result of the COVID-19 pandemic. Temporary closure of routine screening and elective surgery resulted

in increasing theatre waiting lists. Major delays were encountered with engagement and opening of new sites. Research and development (R&D) departments initially prioritised COVID-19-related studies and urgent public health work, with the perception that some sites were subsequently shifting their focus to commercial projects. The resulting backlog of studies caused longer wait times for review and approval of the HELP Fertility? study. Clinical and research staff faced difficulty in attending training sessions and confirming their capacity to conduct the RCT. Situations were further complicated by several additional factors: staff absences due to illness, frequent reassignment of personnel to clinical duties or vaccine distribution efforts and a country-wide scarcity of nurses and midwives with the specialised knowledge in reproductive health and childbirth needed for effective participant recruitment and management. Moreover, the situation was further strained as some research staff reported that they were instructed to use their annual leave during the summer months, reducing availability during this period.

A comprehensive and well-defined site initiation procedure was implemented, with information packages that were well received by the R&D departments at participating sites. All site initiation visits were carried out remotely, with recordings distributed to accommodate the schedules of all staff. Conducting activities, such as site initiation visits and monitoring remotely, due to the pandemic, resulted in some issues with engagement and memorability. An in-person investigator meeting was held in October 2022, with representation from 19 NHS Trusts nationally, the Fertility Network and a public representative. Principal investigators (PIs), associate PIs, research nurses and midwives from open sites and prospective sites attended. The meeting aimed to facilitate discussions among experienced clinicians, share the centralised support approach and enhance the trial's visibility to boost recruitment. A feedback survey received 10 responses, with an average rating of 9.5 for the usefulness of presentations for sites already involved and 9.2 for sites considering participation. Nine respondents expressed their intention to attend future meetings, while one respondent was undecided.

The central team was easily accessible and sent regular communications in newsletters and monthly nurse meetings. Additionally, the central research team introduced a centralised system to support participant recruitment and follow-up remotely.

The challenges related to establishing sites and recruiting participants were exacerbated by the Department of Health and Social Care's Research Reset programme, which was created to assess whether studies would deliver their outcomes to free up research capacity (now replaced by the UK Clinical Research Delivery Programme).[38] Inclusion of the HELP Fertility? study on the 'Reset' list increased uncertainty and risk for sites to proceed with setting up. Due to prolonged decision-making processes, the research team could not provide sites with information about the study's continuity. This decreased site motivation to proceed with set-up and recruitment, potentially resulting in wasted effort. It was observed that Research Reset programme created additional strain on site R&D departments and the research team's capacity at the CTRU.

From August 2022, we were observing an increase in the number of new NHS sites with capacity to open new trials. By February 2023, 16 NHS sites were open to recruitment and a further 6 sites were in set-up, with approvals imminent. The trial was also being opened in the private sector organisation, Care Fertility. During March–September 2022, participant screening and identification rates were seen to be increasing in comparison to the earlier 2021–2 monthly figures. We observed that sites were becoming increasingly confident at approaching new potential participants and confident in trial processes following recruitment of their first one to two participants (*Table 9*).

Despite extensive efforts made by the study team to improve site engagement and recruitment, an insufficient number of participants were recruited within time frames that were set prior to the COVID-19 pandemic. The team proposed a change in trial design to combine the two RCTs (fibroid and polyp population) to a single combined RCT,

**TABLE 9** Participant identification (screened) per month (total of all sites)

| Year | 2021 | | | | | | | | | | 2022 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month | March | April | May | June | July | August | September | October | November | December | January | February | March | April | May | June | July | August |
| Participants identified | 14 | 5 | 3 | 10 | 5 | 4 | 4 | 6 | 5 | 2 | 2 | 8 | 17 | 10 | 19 | 9 | 25 | 17 |

with a reduced sample size of 560. A time extension for delivery would have been required, potentially with the costs unchanged, due to earlier significant cost savings. Trial progress and continuation options were discussed at a formal monitoring meeting with the NIHR–HTA (25 January 2023). The HTA decision to close the trial as part of the NIHR Research Reset Programme was communicated with the Chief Investigator on 24 February 2023. We do not believe that any other actions could have significantly improved the recruitment rate in this project.

### Cost-effectiveness analysis reflections and limitations

The cost-effectiveness analyses are severely limited by the small sample size and the resulting extreme uncertainty. The number of live births observed was low (3/16 participants in the control group, 3/19 participants in the intervention group). In such circumstances, just one additional live birth in either randomised group could have a considerable impact on point estimates of means and cost-effectiveness ratios. Similarly, individual participants who incurred much higher costs than other participants have a substantial impact on results. Therefore, while our analyses seek to illustrate what the data collected suggest about the potential cost-effectiveness of hysteroscopic resection compared to control treatment, all results should be interpreted with extreme caution.

Other limitations of our analysis include the use of resource use questionnaires, which may be subject to recall bias, and our use of a 3-month recall within the questionnaires, which necessitated multiplying reported resource uses in order to estimate costs for the entire study period. This could result in inaccurate cost estimates. However, the main cost driver was that associated with receiving hysteroscopic resection, which was based on data collected in CRFs rather than using resource use questionnaires. In addition, while resource use questionnaires have important limitations, the same approach was used for both treatment groups, and so the impact on relative cost-effectiveness may be minor.

## Patient and public involvement

### *Aim*

This project aimed to meaningfully incorporate the perspectives of people with lived experience of infertility and recurrent miscarriage throughout all project phases – from design and execution to dissemination – ensuring the research generates relevant and beneficial outcomes for those affected by fertility challenges.

### *Methods and outcomes*

Study materials were regularly reviewed by the Reproductive Health Research Public Advisory Panel at STH. Patient-facing materials, in particular the participant information sheet, informed consent form and patient satisfaction questionnaire, were developed with PPI input. This was especially helpful to address the potential participant equipoise barrier. Closedown scenarios were also discussed with this panel, and feedback was given on the proposed communications with existing trial participants.

There were two PPI members who were co-applicants on the grant application. One was a representative from Fertility Network UK, and the other was a nurse with personal experience of the study conditions. They also served as integral members in the Trial Management Group, actively contributing to key decisions and strategic discussions, such as regarding removing the crossover in the trial design.

At the investigator meeting, this representative powerfully illustrated the study's significance by sharing first-hand accounts from patients who had experienced fertility issues. Their presentation not only resonated strongly with attendees but also demonstrated the vital role of PPI in strengthening clinical research.

The team tried to incorporate PPI input into the TSC. One member was recruited, but unfortunately, they were later uncontactable and did not attend any meetings. A replacement member was enrolled, but the trial closed before they were able to attend a meeting.

### *Reflections and critical perspective*

Patient and public involvement helped to shape this study's development and delivery. PPI members' contributions enhanced the accessibility and relevance of study procedures, materials and protocols. The partnership with Fertility Network UK kept the research firmly anchored in patients' lived experiences and needs. Regular review by STH's Reproductive Health Research Public Advisory Panel provided a structured oversight of study materials, while PPI representation on Trial Management Group ensured continuous stakeholder input throughout the project's lifecycle.

## Equality, diversity and inclusion

Of the 35 participants, randomised 24 participants in this study were White. Three participants defined their Ethnicity as Black, Black British, Caribbean or African. Two

were Asian or Asian British, two were mixed or multiple ethnic groups and four were other ethnic groups.

In vitro fertilisation birth rates have been found to be consistently lowest in Black and Asian patients; 23% for Black patients, and 24% for Asian patients, compared to 32% in White patients in 2020–1,[39] which may be related to higher average age at starting treatment.

Participation in the study was limited to individuals with adequate English language proficiency. This restriction was implemented due to concerns about obtaining informed consent, ensuring comprehension of trial procedures and accurately completing surveys. The project team determined that translating participant materials into multiple languages was not viable. The 2021 Census in England and Wales found that 3.1% of people cannot speak English and that a further 17.1% cannot speak English well.[40] This language requirement may have inadvertently excluded some members of ethnic minority communities from participating. It is worth noting that as new clinical trials are developed, there is a growing trend towards considering the translation of study materials to promote broader inclusion.

## Impact and learning

This trial aimed to answer an important clinical question encountered regularly in day-to-day clinical practice. However, the study was hindered by several cultural and logistical problems from which lessons can be learned. First and foremost was the COVID pandemic which for a while brought all elective health services to a near standstill. Fertility services were among the first services to be paused and this led to a significant increase in waiting times once the service resumed. Consequently, there was an increased pressure on patients to proceed with treatment as soon as possible to compensate for the delays experienced. Secondly, we experienced some clinicians with preconceived beliefs either supporting surgery or not.

We believe that both points above could have affected participant's decision-making regarding whether to participate in the trial.

We make the following recommendations;

1. Clinical equipoise should be established among multiple consultants at each site during site feasibility. Support from the senior directorate should be gained to ensure that all potentially eligible participants will be made aware of the research trial and have the opportunity to take part.
2. Approaching patients to explain the trial at the time of diagnosis, rather than after a period of time on a surgery waiting list, is likely to help address to some degree the patient equipoise/trial recruitment barrier.
3. Inclusion and timing of a crossover, plus the impact on patient equipoise, should be carefully considered in future similar trials, especially with time/age critical fertility-related interventions, which can cause much anxiety for participants.

Even though the numbers recruited into this study are small and no robust clinical interpretation can be reached through statistical analysis, within this incomplete study, a similar proportion of participants in both the hysteroscopic resection and no resection groups experienced a live birth within 15 months; the CI for the risk difference or difference in proportions with a live birth is wide, suggesting considerable uncertainty in the estimate, but the data from the trial are consistent with there being no difference in LBRs between the randomised groups (*Figure 4*).

Sample size calculations for this trial were largely based on estimates, as no LBR data were available for the 'no resection' and 'resection' populations. The HELP Fertility? trial is the first to report a LBR, within 15 months for these populations;

Resection 3/19 or 15.8% (95% CI 5.5% to 37.6%).
No resection 3/16 or 18.8% (95% CI 6.6% to 43%).

## Implications for decision-makers

The fertility sector has been permanently changed by the COVID pandemic. Given that there has been no significant change in funding restrictions, patients are still only allowed a very limited number of IVF cycles. There remains significant pressure on both patients and clinicians to proceed with the quickest treatment possible, avoiding any unnecessary delay. Whether or not to proceed with surgery for a small submucous fibroid or polyp before having assisted conception treatment will be highly reliant on the set up of the Health Service, the patient's age and the speed at which different services can be accessed. This is unlikely to change in the future, meaning it would be very difficult to recruit a larger number of participants to a future study that would have sufficient power to enable definitive conclusions to be drawn.

This synopsis should be referenced as follows:
Metwally M, McKendrick K, Ridsdale K, Pye C, Walters S, Amer S, *et al*. Removal of small fibroids and polyps in patients with infertility and recurrent miscarriage: The HELP Fertility? RCT [published online ahead of print February 25 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJMM1915

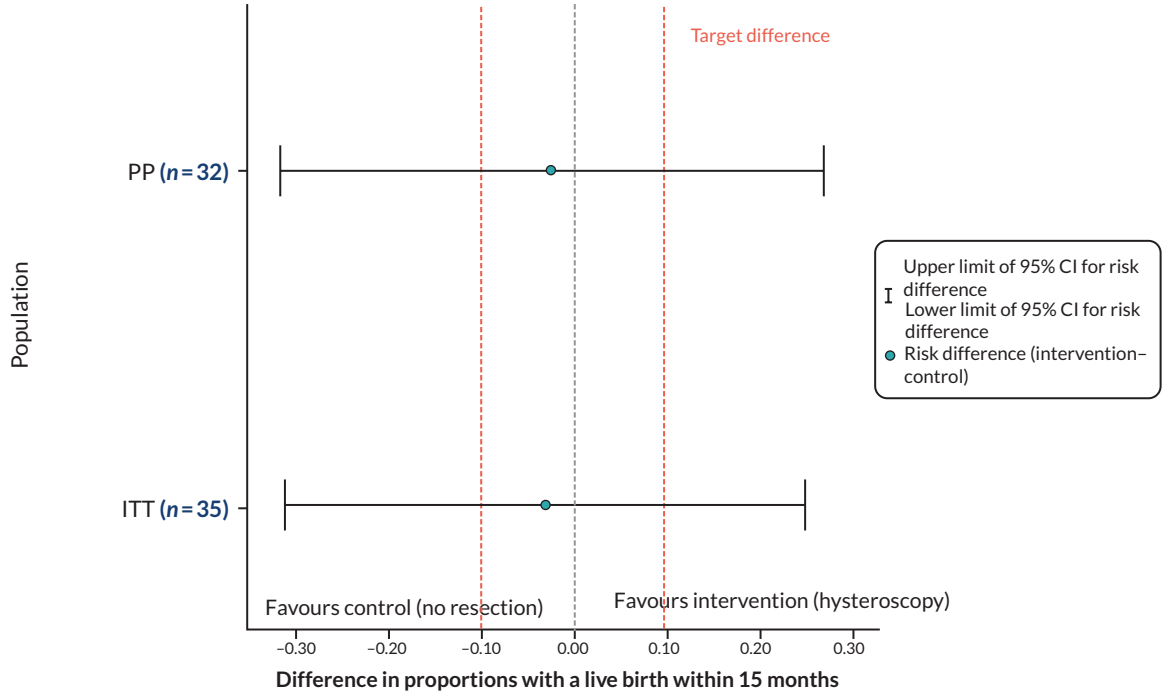


**FIGURE 4** Effect of no resection and resection on LBR within 15 months based on ITT and PP populations.

Treatment of small submucous fibroids and polyps therefore should be left to be decided on a one-to-one basis, depending on the logistics, needs and requirements of each individual patient.

## Research recommendations

The research highlights several critical considerations for future fertility studies:

1. Clinical equipoise must be carefully established among consultants.
2. Participant recruitment is optimised by approaching participants at diagnosis.
3. An integrated clinical–research team approach can facilitate more efficient randomisation and intervention delivery.
4. Trial designs for time-sensitive interventions require careful consideration of participant anxiety and crossover mechanisms.
5. PPI is a crucial component, enhancing study design and maintaining patient-centred focus.

## Conclusions

The HELP Fertility? trial encountered significant recruitment challenges in investigating the impact of hysteroscopic resection on fertility outcomes, primarily due to the COVID-19 pandemic's disruption of healthcare services. Despite recruiting only 35 participants, the study provides valuable insights into clinical research complexities.

Due to the small number of participants recruited, we are unable to conclude with any statistical reliability any difference in the proportions, with a live birth at 15-month follow-up, between surgical intervention and no resection for small submucous fibroids and polyps.

## Additional information

### *CRediT contribution statement*

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**Stephen Walters** (https://orcid.org/0000-0001-9000-8126): Conceptualisation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft, Writing – reviewing and editing.

**Saad Amer** (https://orcid.org/0000-0001-8321-1302): Conceptualisation, Funding acquisition, Investigation, Methodology, Writing – reviewing and editing.

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**Anju Keetharuth** (https://orcid.org/0000-0001-8889-6806): Formal analysis, Visualisation, Writing – original draft, Writing – reviewing and editing.

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## Data-sharing statement

All data requests must be directed to the corresponding author for review. De-identified participant data and statistical code will be provided upon reasonable request. Requests should specify

the required data fields and the purpose of the request, ideally including a protocol or at least a research plan. The data dictionary and statistical analysis plan may also be made available. Each request will be evaluated individually, and requestors will need to complete a data-sharing agreement with the sponsor before any data is transferred.

## Ethics statement

The trial was approved by the West Midlands – Edgbaston Research Ethics Committee on 10 February 2021 (reference 21/WM/0013).

## Information governance statement

The University of Sheffield is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Sheffield is the Data Processor and Sheffield Teaching Hospitals is the Data Controller. We process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for Sheffield Teaching Hospitals Data Protection Officer here: www.sth.nhs.uk/about-us/general-data-protection-regulations.

## Disclosure of interests

***Full disclosure of interests:*** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJMM1915.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

## Trial registration

This trial is registered as Current Controlled Trials ISRCTN 91356224.

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## List of abbreviations

| | |
|---|---|
| CEAC | cost-effectiveness acceptability curve |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CTRU | Clinical Trials Research Unit |
| HELP | Hysteroscopic Excision of Leiomyoma and Polyp |
| HTA | Health Technology Assessment |
| ICER | incremental cost-effectiveness ratio |
| ICSI | intracytoplasmic sperm injection |
| ITT | intention to treat |
| IUI | intrauterine insemination |
| IVF | in vitro fertilisation |
| LBR | live birth rate |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| PI | principal investigator |
| PP | per protocol |
| PPI | patient and public involvement |
| PSS | Personal Social Services |
| PUL | pregnancy of unknown location |
| RCT | randomised controlled trial |
| R&D | research and development |
| STH | Sheffield Teaching Hospitals |
| TSC | Trial Steering Committee |

## References

1. World Health Organization. *Infertility Prevalence Estimates 1990–2021*. 2023. URL: www.who.int/publications/i/item/978920068315 (accessed 12 August 2025).
2. Human Fertilisation and Embryology Authority. *Fertility Treatment 2022: Preliminary Trends and Figures*. 2024. URL: www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2022-preliminary-trends-and-figures/ (accessed 12 August 2025).
3. Regan L, Rai R, Saravelos S, Li TC. Recurrent miscarriage green-top guideline No. 17. *BJOG* 2023;**130**:e9–39. https://doi.org/10.1111/1471-0528.17515
4. Huang H, Kuang H, Sun F, Diamond MP, Legro RS, Coutifaris C, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Reproductive Medicine Network. Lower prevalence of non–cavity-distorting uterine fibroids in patients with polycystic ovary syndrome than in those with unexplained infertility. *Fertil Steril* 2019;**111**:1011–9.e1. https://doi.org/10.1016/j.fertnstert.2019.01.020
5. Izhar R, Husain S, Tahir S, Husain S. Incidence of intrauterine abnormalities in Pakistani women with unexplained infertility diagnosed via saline infusion sonography. *J Ultrason* 2018;**18**:186–92. https://doi.org/10.15557/JoU.2018.0028
6. Jayakrishnan K, Menon V, Nambiar D. Submucous fibroids and infertility: effect of hysteroscopic myomectomy and factors influencing outcome. *J Hum Reprod Sci* 2013;**6**:35. https://doi.org/10.4103/0974-1208.112379
7. Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. *Fertil Steril* 2011;**95**:2690–2. https://doi.org/10.1016/j.fertnstert.2010.12.034
8. Al Chami A, Saridogan E. Endometrial polyps and subfertility. *J Obstet Gynecol India* 2017;**67**:9–14. https://doi.org/10.1007/s13224-016-0929-4
9. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 2009;**91**:1215–23. https://doi.org/10.1016/j.fertnstert.2008.01.051

10. Moon JW, Kim CH, Kim JB, Kim SH, Chae HD, Kang BM. Alterations in uterine hemodynamics caused by uterine fibroids and their impact on in vitro fertilization outcomes. *Clin Exp Reprod Med* 2015;**42**:163–8. https://doi.org/10.5653/cerm.2015.42.4.163

11. Bosteels J, van Wessel S, Weyers S, Broekmans FJ, D'Hooghe TM, Bongers MY, *et al*. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database Syst Rev* 2018;**12**:CD009461. https://doi.org/10.1002/14651858.CD009461.pub4

12. Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. *Cochrane Database Syst Rev* 2012;**11**:CD003857. https://doi.org/10.1002/14651858.cd003857.pub3

13. Lőrincz J, Molnár S, Jakab A, Herman T, Jashanjeet S, Török P. The effect of localization and histological verification of endometrial polyps on infertility. *Arch Gynecol Obstet* 2019;**300**:217–21. https://doi.org/10.1007/s00404-019-05155-3

14. Kalampokas T, Tzanakaki D, Konidaris S, Iavazzo C, Kalampokas E, Gregoriou O. Endometrial polyps and their relationship in the pregnancy rates of patients undergoing intrauterine insemination. *Clin Exp Obstet Gynecol* 2012;**39**:299–302.

15. Karakuş SS, Özdamar O, Karakuş R, Gün I, Sofuoğlu K, Muhcu M, Polat M. Reproductive outcomes following hysteroscopic resection of endometrial polyps of different location, number and size in patients with infertility. *J Obstet Gynaecol* 2016;**36**:395–8. https://doi.org/10.3109/01443615.2015.1085847

16. Check JH, Bostick-Smith CA, Choe JK, Amui J, Brasile D. Matched controlled study to evaluate the effect of endometrial polyps on pregnancy and implantation rates following in vitro fertilization-embryo transfer (IVF-ET). *Clin Exp Obstet Gynecol* 2011;**38**:206–8.

17. Elias RT, Pereira N, Karipcin FS, Rosenwaks Z, Spandorfer SD. Impact of newly diagnosed endometrial polyps during controlled ovarian hyperstimulation on invitro fertilization outcomes. *J Minim Invasive Gynecol* 2015;**22**:590–4. https://doi.org/10.1016/j.jmig.2014.12.170

18. Ghaffari F, Arabipoor A, Bagheri Lankarani N, Hosseini F, Bahmanabadi A. Hysteroscopic polypectomy without cycle cancellation in IVF/ICSI cycles: a cross-sectional study. *Eur J Obstet Gynecol Reprod Biol* 2016;**205**:37–42. https://doi.org/10.1016/j.ejogrb.2016.08.019

19. Stamatellos I, Apostolides A, Stamatopoulos P, Bontis J. Pregnancy rates after hysteroscopic polypectomy depending on the size or number of the polyps. *Arch Gynecol Obstet* 2008;**277**:395–9. https://doi.org/10.1007/s00404-007-0460-z

20. Tiras B, Korucuoglu U, Polat M, Zeyneloglu HB, Saltik A, Yarali H. Management of endometrial polyps diagnosed before or during ICSI cycles. *Reprod Biomed Online* 2012;**24**:123–8. https://doi.org/10.1016/j.rbmo.2011.09.002

21. Zhu H, Fu J, Lei H, Song Y, Shen L, Huang W. Evaluation of transvaginal sonography in detecting endometrial polyps and the pregnancy outcome following hysteroscopic polypectomy in infertile women. *Exp Ther Med* 2016;**12**:1196–200. https://doi.org/10.3892/etm.2016.3407

22. Afifi K, Anand S, Nallapeta S, Gelbaya TA. Management of endometrial polyps in subfertile women: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2010;**151**:117–21. https://doi.org/10.1016/j.ejogrb.2010.04.005

23. Zhang H, He X, Tian W, Song X, Zhang H. Hysteroscopic resection of endometrial polyps and assisted reproductive technology pregnancy outcomes compared with no treatment: a systematic review. *J Minim Invasive Gynecol* 2019;**26**:618–27. https://doi.org/10.1016/j.jmig.2018.10.024

24. National Institute for Health and Care Excellence. *Fertility Problems: Assessment and Treatment*. 2017. URL: www.nice.org.uk/guidance/cg156/resources/fertility-problems-assessment-and-treatment-35109634660549 (accessed 5 August 2025).

25. Dreisler E, Kjer JJ. Asherman's syndrome: current perspectives on diagnosis and management. *Int J Womens Health* 2019;**11**:191–8. https://doi.org/10.2147/IJWH.S165474

26. Propst AM, Liberman RF, Harlow BL, Ginsburg ES. Complications of hysteroscopic surgery: predicting patients at risk. *Obstet Gynecol* 2000;**96**:517–20. https://doi.org/10.1016/S0029-7844(00)00958-3

27. Salazar CA, Isaacson K, Morris S. A comprehensive review of Asherman's syndrome. *Curr Opin Obstet Gynecol* 2017;**29**:249–56. https://doi.org/10.1097/gco.0000000000000378

28. Gambadauro P, Navaratnarajah R, Carli V. Anxiety at outpatient hysteroscopy. *Gynecol Surg* 2015;**12**:189–96. https://doi.org/10.1007/s10397-015-0895-3

29. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med* 2017;**377**:62–70. https://doi.org/10.1056/NEJMra1510062

30. Avery KNL, Williamson PR, Gamble C, Francischetto EOC, Metcalfe C, Davidson P, *et al*. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;**7** e013537. https://doi.org/10.1136/bmjopen-2016-013537

31. World Health Organization. *Safe Surgery: Tool and Resources | WHO Surgical Safety Checklist*. 2025. URL: www.who.int/teams/integrated-health-services/patient-safety/research/safe-surgery/tool-and-resources (accessed 12 August 2025).

32. National Institute for Health and Care Excellence. *NICE Health Technology Evaluations: The Manual (PMG36). Process Methods*. 2022. URL: www.nice.org.uk/process/pmg36/ (accessed 12 August 2025).

33. NHS England. *National Cost Collection for the NHS*. 2025. URL: www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed 12 August 2025).

34. Jones KC, Weatherley H, Birch S, Castelli A, Chalkley M, Dargan A, *et al*. Unit Costs of Health & Social Care 2023 manual. Kent, UK: Personal Social Services Research Unit & Centre for Health Economics; 2024.

35. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, *et al*.; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Clin Ther* 2022;**44**:158–68. https://doi.org/10.1016/j.jval.2021.11.1351

36. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997;**6**:327–40. https://doi.org/10.1002/(sici)1099-1050(199707)6:4<327::aid-hec282>3.0.co;2-w

37. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. *Econ Eval Clin Trials* 2014. https://doi.org/10.1093/med/9780199685028.001.0001

38. *UK Clinical Research Delivery Programme (UKCRD)*. URL: https://sites.google.com/nihr.ac.uk/thefutureofuk-clinicalresearch/home (accessed 9 September 2025).

39. Human Fertilisation & Embryology Authority. *Ethnic Diversity in Fertility Treatment 2021*. 2021. URL: www.hfea.gov.uk/about-us/publications/research-and-data/ethnic-diversity-in-fertility-treatment-2021/ (accessed 12 August 2025).

40. Office for National Statistics. *Language, England and Wales: Census 2021*. 2024. URL: www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/language/bulletins/languageenglandandwales/census2021 (accessed 12 August 2025).

# Appendix 1 Figures and tables

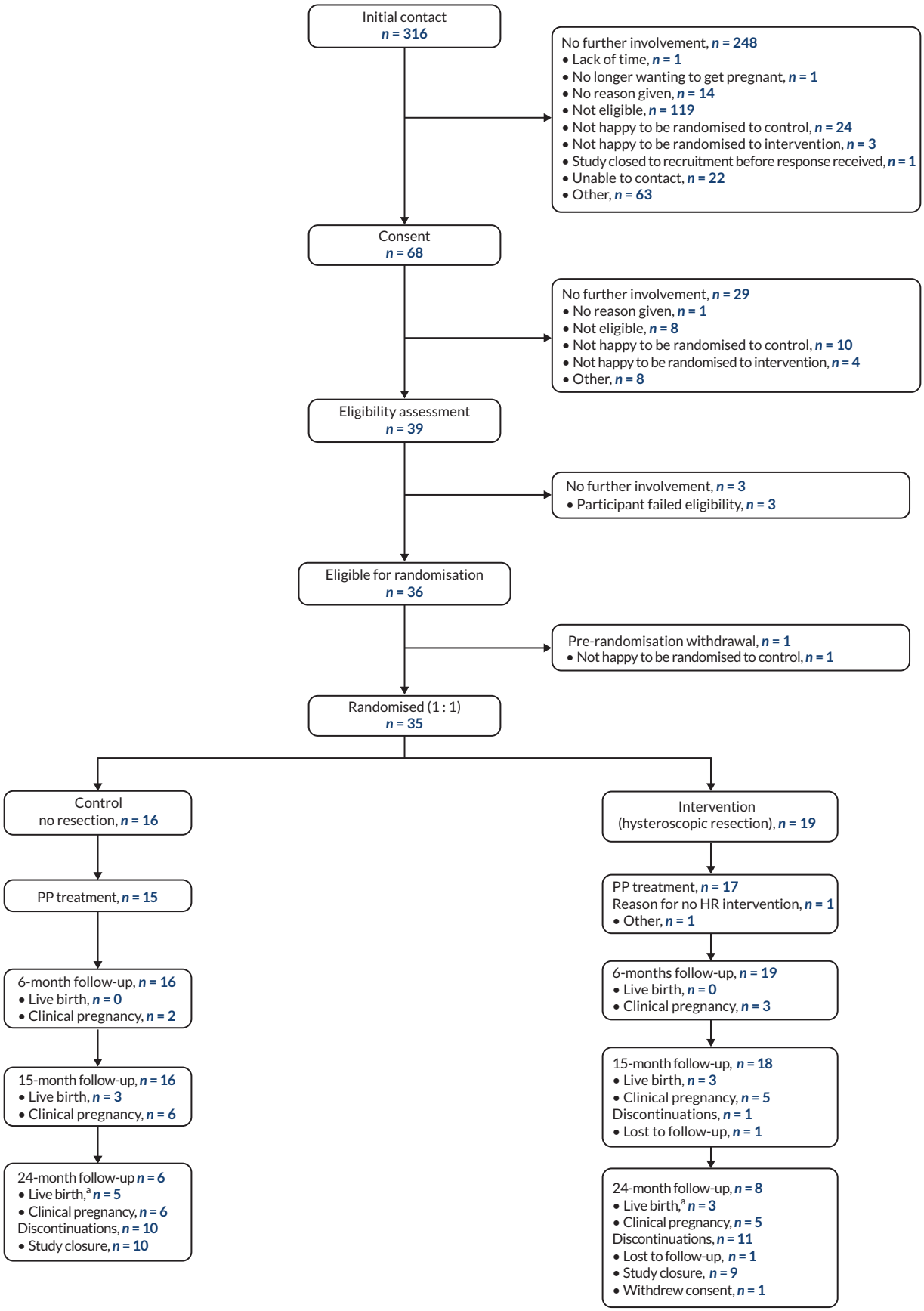



**FIGURE 5** The HELP Fertility? Study Consolidated Standards of Reporting Trials diagram. Outcome and discontinuation numbers are cumulative. a, Two participants (one in each arm) experienced a live birth after their 15 months follow-up and before study closure, but due to the closure of the study, these participants did not receive a 24 months follow-up. These two live births are excluded from the 24 months follow-up outcomes. HR, hazard ratio.

**TABLE 10** Unit costs in the cost-effectiveness analysis

| Resource use | Sheet/table no.[a,b] | Currency code | Unit costs £ |
|---|---|---|---|
| GP – at surgery[a] | Table 9.4.2 | – | 49.00 |
| GP – at home[a] | Assumed equal to surgery cost | – | 49.00 |
| GP – via phone/e-mail[a] | Table 9.5.1 | – | 43.92 |
| GP – via video call[a] | Table 9.5.2 | – | 43.92 |
| Practice nurse – at surgery[a] | Table 9.5.3 | – | 8.83 |
| Practice nurse – via phone/e-mail[a] | Table 9.5.3 | – | 8.83 |
| Dentist – in clinic[a] | Table 9.8 | – | 55.50 |
| Pharmacist – in clinic[a] | Table 12.3.6; Table 8.2.1 with rates | – | 13.25 |
| Health visitor – clinic[b] | Community health services | N12, N03B, N03D, N03E, N03F, N03C | 104.09 |
| Health visitor – home[b] | Community health services | N12, N03B, N03D, N03E, N03F, N03C | 104.09 |
| Community psychiatric/mental health nurse[a] | Table 9.2.1 | – | 32.00 |
| Midwife – clinic[b] | Total outpatient attendances | Service code 560 | 125.00 |
| Midwife – phone[b] | Assumed to be 25% of clinic cost | – | 31.25 |
| A&E[b] | Emergency care | VB09Z, VB08Z, VB99Z, VB06Z, VB07Z, VB05Z, VB03Z, VB04Z, VB01Z, VB02Z | 121.07 |
| Planned hospital visits – outpatients[b] | Total outpatient attendances | Service codes 501–502 | 172.20 |
| Planned hospital visits – day case[b] | Total outpatient attendances | MB09* codes, MC07Z, MC08Z, MC09Z, MC10Z, MC11Z, MC12Z, MC13Z, MC14Z, MC20Z, MC21Z | 1607.88 |
| Planned hospital visits – scans[b] | Outpatient procedures | NZ21Z, Service codes 501, 502, 560 | 195.13 |
| Planned hospital visits – consultant-led appointment[b] | Total outpatient attendances | Service codes 501–502 | 212.33 |
| Planned hospital visits – non-consultant-led appointment[b] | Total outpatient attendances | Service code 501–502 | 145.70 |
| Planned hospital visits – oocyte recovery[b] | Admitted patient care – Day case | MC12Z | 2416.58 |
| Planned hospital visits – hysterosalpingography[b] | Outpatient procedures | MA44Z | 379.87 |
| Planned hospital visits – implantation of embryo[b] | Outpatient procedures | MC11Z | 837.12 |
| Planned hospital visits – minor laparoscopic surgery[b] | Outpatient procedures | MA10Z | 276.06 |
| Planned hospital visits – blood test[b] | Directly accessed pathology services | DAPS08 | 6.41 |
| Planned hospital visits – diagnostic hysteroscopy biopsy[b] | Outpatient procedures | MA32Z | 343.90 |
| Other NHS services – counselling[b] | Mental healthcare contact | C02 | 296.99 |
| Other NHS services – oocyte recovery with ICSI[b] | Outpatient procedures | MC14Z | 6058.61 |
| Other NHS services – ophthalmology[b] | Total outpatient attendances | Service code 130 | 135.00 |
| Other NHS services – dermatology[b] | Total outpatient attendances | Service code 330 | 161.00 |
| Non-elective inpatient[b] | Admitted patient care – non-elective | MA* codes | 5571.06 |

a PSSRU 2024 Unit costs 2022/2023.
b National Schedule of NHS costs 2022/23.

**TABLE 11** Baseline demographic and other characteristics of participants

| Variable | Level/statistic | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|---|
| City/town (of fertility centre) | Aberdeen | 0 (0%) | 3 (16%) | 3 (9%) |
| | Dundee | 1 (6%) | 1 (5%) | 2 (6%) |
| | London | 0 (0%) | 1 (5%) | 1 (3%) |
| | Manchester | 1 (6%) | 1 (5%) | 2 (6%) |
| | Newcastle | 3 (19%) | 3 (16%) | 6 (17%) |
| | Rotherham | 0 (0%) | 1 (5%) | 1 (3%) |
| | Sheffield | 8 (50%) | 7 (37%) | 15 (43%) |
| | Southampton | 2 (12%) | 0 (0%) | 2 (6%) |
| | Stockton-on-Tees | 1 (6%) | 2 (11%) | 3 (9%) |
| Trial | Endometrial polyps | 12 (75%) | 13 (68%) | 25 (71%) |
| | Submucous fibroids | 4 (25%) | 6 (32%) | 10 (29%) |
| Age (years) | Mean (SD) | 35 (4) | 37 (5) | 36 (5) |
| | Median (IQR) | 36 (33–38) | 38 (32–41) | 37 (32–40) |
| | Minimum–maximum | 25–40 | 27–44 | 25–44 |
| Ethnicity[a] | Asian or Asian British | 1 (6%) | 1 (5%) | 2 (6%) |
| | Black, Black British, Caribbean, or African | 0 (0%) | 3 (16%) | 3 (9%) |
| | Mixed or multiple ethnic groups | 1 (6%) | 1 (5%) | 2 (6%) |
| | White | 13 (81%) | 11 (58%) | 24 (69%) |
| | Other ethnic group | 1 (6%) | 3 (16%) | 4 (11%) |
| Current smoker[b] | No | 16 (100%) | 19 (100%) | 35 (100%) |
| Current recreational drug user | No | 16 (100%) | 19 (100%) | 35 (100%) |
| Current consumer of alcohol | No | 9 (56%) | 13 (68%) | 22 (63%) |
| | Yes | 7 (44%) | 6 (32%) | 13(37%) |
| Alcohol consumption (units per week) | Mean (SD) | 2.1 (3.3) | 0.9 (1.6) | 1.5 (2.6) |
| | Median (IQR) | 0.0 (0.0–3.2) | 0.0 (0.0–2.0) | 0.0 (0.0–2.0) |
| | Minimum–maximum | 0.0–10.0 | 0.0–6.0 | 0.0–10.0 |
| BMI (kg/m$^2$) | Mean (SD) | 24.1 (4.4) | 24.8 (4.1) | 24.5 (4.2) |
| | Median (IQR) | 23.1 (20.5–28.3) | 23.9 (22.5–27.4) | 23.3 (21.1–27.4) |
| | Minimum–maximum | 18.3–32.0 | 16.5–33.0 | 16.5–33.0 |
| History of infertility or recurrent miscarriage | Infertility | 15 (94%) | 18 (95%) | 33 (94%) |
| | Recurrent miscarriage | 1 (6%) | 1 (5%) | 2 (6%) |
| Previous fertility treatment received[c] | None | 12 (75%) | 10 (53%) | 22 (63%) |
| | IVF/ICSI/Frozen Embryo Replacement | 4 (25%) | 8 (42%) | 12 (34%) |
| | IUI | 0 (0%) | 3 (16%) | 3 (9%) |
| | Ovulation | 1 (6%) | 0 (0%) | 1 (3%) |
| | Other | 1 (6%) | 1 (5%) | 2 (6%) |

**TABLE 11** Baseline demographic and other characteristics of participants (*continued*)

| Variable | Level/statistic | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|---|
| Number of previous pregnancies | 0 | 8 (50%) | 9 (47%) | 17 (49%) |
| | 1 | 4 (25%) | 5 (26%) | 9 (26%) |
| | 2 | 1 (6%) | 2 (11%) | 3 (9%) |
| | 3 | 2 (12%) | 1 (5%) | 3 (9%) |
| | ≥ 4 | 1 (6%) | 2 (11%) | 3 (9%) |
| Number of previous miscarriages | 0 | 11 (69%) | 12 (63%) | 23 (66%) |
| | 1 | 1 (6%) | 4 (21%) | 5 (14%) |
| | 2 | 1 (6%) | 2 (11%) | 3 (9%) |
| | ≥ 3 | 3 (19%) | 1 (5%) | 4 (11%) |
| Parity[d] | 0 | 13 (81%) | 14 (74%) | 27 (77%) |
| | 1 | 3 (19%) | 2 (11%) | 5 (14%) |
| | 2 | 0 (0%) | 2 (11%) | 2 (6%) |
| | ≥ 3 | 0 (0%) | 1 (5%) | 1 (3%) |

IQR, interquartile range; SD, standard deviation.
a Ethnicity groups as used in the 2021 Census in England and Wales.
b Only relates to smoking cigarettes, excludes vaping.
c May sum to more than the total number of participants since participants may have received more than one type of fertility treatment.
d Includes five live births with unknown gestational age.

**TABLE 12** Primary outcome sensitivity analysis (PP population)

| Outcome | Control (no resection) (*n* = 15) | Intervention (hysteroscopic resection) (*n* = 17) | RD[a] (95% CI) | RR (95% CI) | OR (95% CI) |
|---|---|---|---|---|---|
| Participant who experienced a live birth within 15 months | 3 (20.0%) | 3 (17.6%) | −2.4 % (−31.9% to 27.2%) | 0.88 (0.21 to 3.73) | 0.86 (0.15 to 5.06) |

a (Absolute) RD (difference in percentage of participants who experienced a live birth within 15 months).

**Note**
Control (no resection) is the reference group.

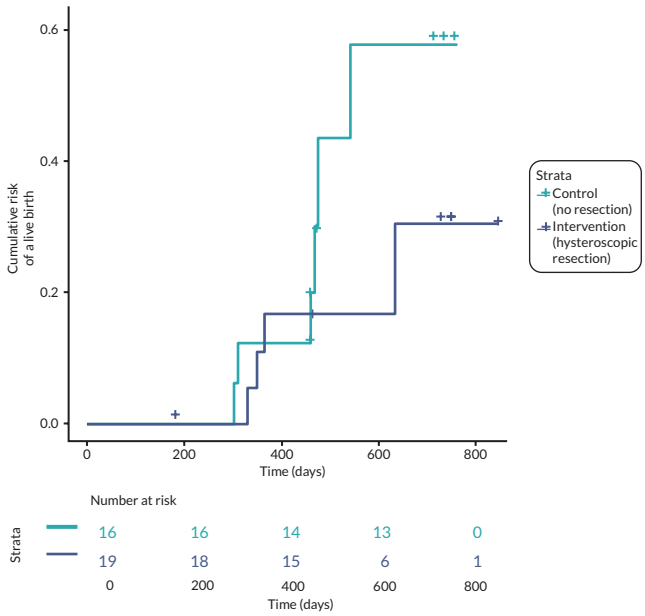
**TABLE 13** Adjusted outcome, ITT population

| Analysis | Hazard ratio (95% CI) |
|---|---|
| Time to first live birth, ITT | 0.53 (0.15 to 1.89) |
| Time to first live birth, PP | 0.57 (0.16 to 2.04) |
| Time to first clinical pregnancy, ITT | 0.65 (0.20 to 2.15) |
| Time to first clinical pregnancy, PP | 0.69 (0.21 to 2.26) |

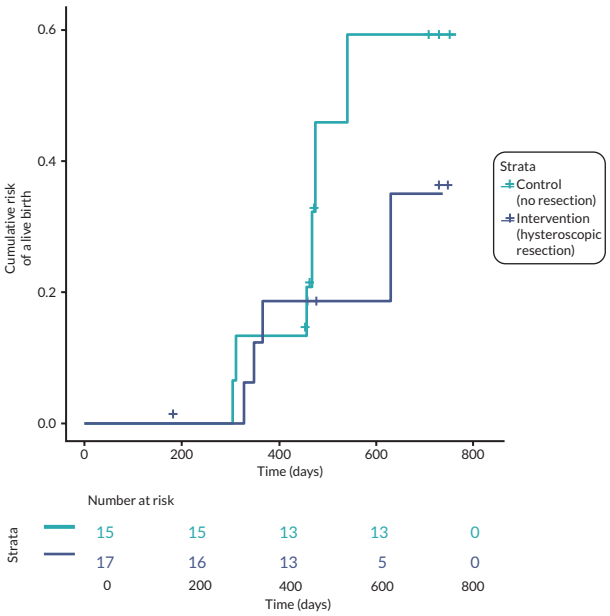
**TABLE 14** Time-to-event analyses estimated hazard ratios

| Outcome | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | Unadjusted RR (95% CI) | Adjusted RR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|---|
| Participant who experienced a live birth within 15 months | 3 (18.8%) | 3 (15.8%) | 0.84 (0.20 to 3.61) | 0.84 (0.20 to 3.59) | 0.81 (0.14 to 4.72) | 0.83 (0.14 to 4.92) |

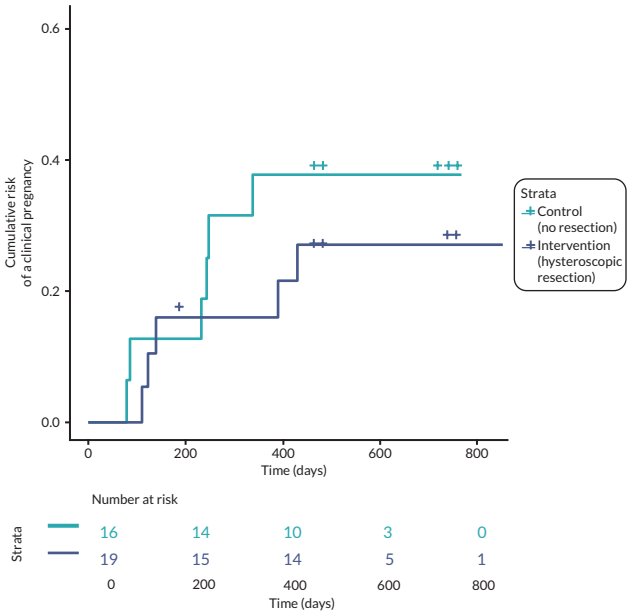
**Note**
Control (no resection) is the reference group.



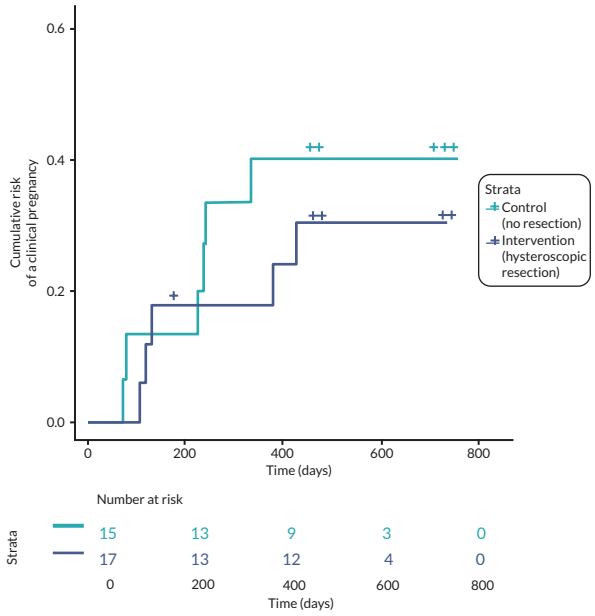

(a) Time to first live birth, ITT




(b) Time to first live birth, PP




(c) Time to first clinical pregnancy, ITT




(d) Time to first clinical pregnancy, PP

**FIGURE 6** Kaplan–Meier plots of time-to-event analyses.

**TABLE 15** Details of hysteroscopic resection procedure(s) received by all participants who received hysteroscopic resection

| Variable | Level/statistic | Endometrial polyps (*n* = 16) | Submucous fibroids (*n* = 6) | All (*n* = 22) |
|---|---|---|---|---|
| Number of hysteroscopic procedures per participant | 1 | 16 (100%) | 4 (67%) | 20 (91%) |
| | 2 | 0 (0%) | 2 (33%) | 2 (9%) |
| Diagnosis of polyps/fibroids confirmed visually during procedure? | Yes | 14 (88%) | 4 (67%) | 18 (82%) |
| | No | 0 (0%) | 2 (33%) | 2 (9%) |
| | Not recorded | 2 (12%) | 0 (0%) | 2 (9%) |
| Diagnosis of polyps/fibroids confirmed by histology? | Yes | 13 (81%) | 4 (67%) | 17 (77%) |
| | No | 2 (12%) | 2 (33%) | 4 (18%) |
| | Not recorded | 1 (6%) | 0 (0%) | 1 (5%) |
| Number of weeks post surgery abstaining from sexual intercourse[a] | Mean (SD) | 3.9 (4.1) | 5.0 (2.4) | 4.2 (3.5) |
| | Median (IQR) | 2.0 (1.0–6.3) | 4.5 (3.0–7.2) | 3.0 (1.4–7.2) |
| | Minimum–maximum | 1.0–12.0 | 3.0–8.0 | 1.0–12.0 |
| Type of resection/removal device used[b] | Bipolar resectoscope | 1 (6%) | 2 (33%) | 3 (14%) |
| | Hysteroscopic morcellator | 5 (31%) | 1 (17%) | 6 (27%) |
| | Monopolar resectoscope | 2 (12%) | 1 (17%) | 3 (14%) |
| | Polyp snares | 2 (12%) | 0 (0%) | 2 (9%) |
| | Other | 4 (25%) | 2 (33%) | 6 (27%) |
| | Not recorded | 1 (6%) | 0 (0%) | 1 (5%) |
| | Not applicable | 1 (6%) | 1 (17%) | 2 (9%) |
| Total size of polyps/fibroids < 3 cm?[c] | Yes | 13 (81%) | 4 (67%) | 17 (77%) |
| | Not recorded | 2 (12%) | 0 (0%) | 2 (9%) |
| | Not applicable | 1 (6%) | 2 (33%) | 3 (14%) |
| Types of submucous fibroids present | Type 1 (50% within cavity) | 0 (0%) | 4 (67%) | 4 (18%) |
| | Not recorded | 0 (0%) | 2 (33%) | 2 (9%) |
| | Not applicable | 16 (100%) | 0 (0%) | 16 (73%) |

a Based on a sample of participants in the intervention arm only (eight endometrial polyps participants; four submucous fibroids participants).
b May sum to more than the total number of participants since participants may have received more than one procedure.
c 'Not applicable' indicates participants for whom no polyps or fibroids were identified during any hysteroscopic procedure.

**TABLE 16** Location of endometrial polyps or submucous fibroids among all participants who received hysteroscopic resection by the trial to which they were recruited

| Location of polyps or fibroids[a] | Endometrial polyps (*n* = 16) | Submucous fibroids (*n* = 6) |
|---|---|---|
| Cornual | 3 (19%) | 0 (0%) |
| Fundal | 1 (6%) | 0 (0%) |
| Lower lateral | 0 (0%) | 1 (17%) |
| Lower posterior | 0 (0%) | 2 (33%) |
| Mid anterior | 2 (12%) | 0 (0%) |
| Mid lateral | 2 (12%) | 2 (33%) |
| Mid posterior | 3 (19%) | 0 (0%) |
| Upper anterior | 2 (12%) | 0 (0%) |
| Upper lateral | 2 (12%) | 0 (0%) |
| Not applicable/recorded | 2 (12%) | 3 (50%) |

a Polyps or fibroids may be present in more than one location, hence values may sum to more than total number of participants in each trial.

**TABLE 17** Details of the methods used to diagnose and accurately measure endometrial polyps or submucous fibroids among all randomised participants

| Variable | Method | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|---|
| Methods of diagnosing the presence of fibroids or polyps | 2D ultrasound | 8 (50%) | 11 (58%) | 19 (54%) |
| | 3D ultrasound | 2 (12%) | 2 (11%) | 4 (11%) |
| | CT/MRI | 1 (6%) | 0 (0%) | 1 (3%) |
| | HyCoSy | 0 (0%) | 1 (5%) | 1 (3%) |
| | Hysterosalpingography | 2 (12%) | 0 (0%) | 2 (6%) |
| | Hysteroscopy | 1 (6%) | 0 (0%) | 1 (3%) |
| | Saline sonography | 2 (12%) | 5 (26%) | 7 (20%) |
| Method of accurately measuring the polyps or fibroids | 2D ultrasound | 13 (81%) | 16 (84%) | 29 (83%) |
| | 3D ultrasound | 3 (19%) | 3 (16%) | 6 (17%) |

MRI, magnetic resonance imaging.

**TABLE 18** Characteristics of the fertility treatments received by randomised participants before their 6 months post-randomisation follow up contact

| Variable | Option | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|---|
| Type of fertility treatment | ART | 4 (25%) | 8 (42%) | 12 (34%) |
| | Ovulation induction | 0 (0%) | 1 (5%) | 1 (3%) |
| | Expectant management | 1 (6%) | 2 (11%) | 3 (9%) |
| Type of ART received | IUI | 0 (0%) | 1 (5%) | 1 (3%) |
| | IVF/ICSI | 2 (12%) | 3 (16%) | 5 (14%) |
| | Transfer of pre-existing frozen/donor embryos | 2 (12%) | 4 (21%) | 6 (17%) |
| Method of ovulation induction | Fertility drugs | 0 (0%) | 1 (5%) | 1 (3%) |
| Ovarian stimulation required? (Only for IUI or IVF/ICSI) | Yes | 1 (6%) | 3 (16%) | 4 (11%) |
| | No | 1 (6%) | 1 (5%) | 2 (6%) |
| Donor sperm required? (Only for IUI, IVF/ICSI or fertilisation or pre-existing frozen/donor eggs) | Yes | 0 (0%) | 1 (5%) | 1 (3%) |
| | No | 2 (12%) | 3 (16%) | 5 (14%) |
| Insemination completed successfully? (Only for IUI) | Yes | 0 (0%) | 1 (5%) | 1 (3%) |
| IVF treatment protocol followed. (Only for IVF/ICSI) | Antagonist | 1 (6%) | 2 (11%) | 3 (9%) |
| | Long | 1 (6%) | 0 (0%) | 1 (3%) |
| | Flare | 0 (0%) | 1 (5%) | 1 (3%) |
| Eggs fertilised? (Only for IVF/ICSI or fertilisation of pre-existing frozen/donor eggs) | Yes | 2 (12%) | 3 (16%) | 5 (14%) |
| Embryo transfer? | Yes | 0 (0%) | 3 (16%) | 3 (9%) |
| | No | 1 (6%) | 0 (0%) | 1 (3%) |
| Type of embryo transfer | Fresh | 0 (0%) | 2 (11%) | 2 (6%) |
| | Frozen | 0 (0%) | 1 (5%) | 1 (3%) |
| Number of embryos transferred | 1 | 0 (0%) | 2 (11%) | 2 (6%) |
| | 2 | 0 (0%) | 1 (5%) | 1 (3%) |

**TABLE 19** Characteristics of the fertility treatments received by randomised participants between their 6- and 15-month post-randomisation follow-up contacts

| Variable | Option | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|---|
| Type of fertility treatment | ART | 10 (62%) | 7 (37%) | 17 (49%) |
| | Expectant management | 1 (6%) | 1 (5%) | 2 (6%) |
| Type of ART received | IUI | 1 (6%) | 0 (0%) | 1 (3%) |
| | IVF/ICSI | 7 (44%) | 6 (32%) | 13 (37%) |
| | Transfer of pre-existing frozen/donor embryos | 3 (19%) | 4 (21%) | 7 (20%) |
| Ovarian stimulation required? (Only for IUI or IVF/ICSI) | Yes | 6 (38%) | 6 (32%) | 12 (34%) |
| | No | 2 (12%) | 0 (0%) | 2 (6%) |
| Donor sperm required? (Only for IUI, IVF/ICSI, or fertilisation of pre-existing frozen/donor eggs) | Yes | 1 (6%) | 0 (0%) | 1 (3%) |
| | No | 6 (38%) | 6 (32%) | 12 (34%) |
| Insemination completed successfully? (Only for IUI) | Yes | 1 (6%) | 0 (0%) | 1 (3%) |
| IVF treatment protocol followed. (Only for IVF/ICSI) | Antagonist | 4 (25%) | 5 (26%) | 9 (26%) |
| | Long | 0 (0%) | 1 (5%) | 1 (3%) |
| | Ultralong | 1 (6%) | 0 (0%) | 1 (3%) |
| | Flare | 2 (12%) | 0 (0%) | 2 (6%) |
| Eggs fertilised? (Only for IVF/ICSI or fertilisation of pre-existing frozen/donor eggs) | Yes | 7 (44%) | 5 (26%) | 12 (34%) |
| | No | 0 (0%) | 1 (5%) | 1 (3%) |
| Embryo transfer? | Yes | 5 (31%) | 4 (21%) | 9 (26%) |
| | No | 2 (12%) | 1 (5%) | 3 (9%) |
| Type of embryo transfer | Fresh | 5 (31%) | 4 (21%) | 9 (26%) |
| Number of embryos transferred | 1 | 3 (19%) | 2 (11%) | 5 (14%) |
| | 2 | 2 (12%) | 2 (11%) | 4 (11%) |

**Notes**
No fertility treatments were recorded for any participants after their 15-month post-randomisation follow-up contact.
If a participant received more than one treatment option in a given period, they contribute (one) to the count of each treatment option they received.

**TABLE 20** Characteristics of embryos transferred during fertility treatment initiated before participants' 6-month post-randomisation follow-up contacts

| Embryo characteristics | Level | Control (no resection) (*n* = 2) | Intervention (hysteroscopic resection) (*n* = 8) | All (*n* = 10) |
|---|---|---|---|---|
| Stage | Cleavage | 0 (0%) | 3 (38%) | 3 (30%) |
| | Blastocyst | 2 (100%) | 5 (62%) | 7 (70%) |
| Grade | Excellent | 2 (100%) | 1 (12%) | 3 (30%) |
| | Moderate | 0 (0%) | 3 (38%) | 3 (30%) |
| | Poor | 0 (0%) | 1 (12%) | 1 (10%) |
| | Unknown/not assessable | 0 (0%) | 3 (38%) | 3 (30%) |

**Note**
The unit of analysis is the (transferred) embryo.

**TABLE 21** Characteristics of embryos transferred during fertility treatment initiated between participants' 6- and 15-month post-randomisation follow-up contacts

| Embryo characteristics | Level | Control (no resection) (*n* = 10) | Intervention (hysteroscopic resection) (*n* = 11) | All (*n* = 21) |
|---|---|---|---|---|
| Stage | Cleavage | 1 (10%) | 1 (9%) | 2 (10%) |
| | Morula | 1 (10%) | 0 (0%) | 1 (5%) |
| | Blastocyst | 8 (80%) | 10 (91%) | 18 (86%) |
| Grade | Excellent | 4 (40%) | 4 (36%) | 8 (38%) |
| | Moderate | 4 (40%) | 2 (18%) | 6 (29%) |
| | Poor | 1 (10%) | 2 (18%) | 3 (14%) |
| | Unknown/not assessable | 1 (10%) | 3 (27%) | 4 (19%) |

**TABLE 22** COVID-19 vaccination status of participants

| Received two or more doses of a COVID-19 vaccination? | Control (no resection) (*n* = 16) | Intervention (hysteroscopic resection) (*n* = 19) | All (*n* = 35) |
|---|---|---|---|
| Yes | 15 (94%) | 16 (84%) | 31 (89%) |
| No | 1 (6%) | 3 (16%) | 4 (11%) |

**Note**
The unit of analysis is the (transferred) embryo.

## Appendix 2 Cost-effectiveness analysis: complete case analysis

The mean costs were £7920 in the hysteroscopic resection group when compared with £3960 in the control group (mean difference £3960, 95% CI £258 to £7720). For every 1000 women treated, the intervention would result in 50 fewer live births than the control group, with 95% CIs ranging from 433 fewer live births to 317 additional live births. Therefore, as for the ITT analysis, at the mean, hysteroscopic resection resulted in fewer live births, but increased costs. This results in a negative ICER of −£79, again implying that hysteroscopic resection is not cost-effective compared to the control treatment and an additional £79,000 would be incurred for every live birth lost. However, again, due to the small sample size, these results are extremely uncertain. CIs for the incremental LBR spanned zero – indicating that there is a chance that the intervention could increase the LBR.

*Appendix 2*, *Figure 7* presents the cost-effectiveness plane for the complete case analysis. In 58% of the bootstrap samples, the control treatment represented a dominant strategy – resulting in a higher LBR and lower costs. In 0.04% of samples, hysteroscopic resection was dominant. In 40% of samples, hysteroscopic resection resulted in a higher LBR and higher costs.

In *Appendix 2*, *Figure 7*, we have again indicated the region of the plot that contains 95% of the bootstrap samples using two red lines beginning at the origin of the graph. Bootstrap samples that lie above these lines fall within the 95% CI. In this analysis, the bounds of the CI include positive and negative ICERs. Because negative ICERs have completely different interpretations depending upon the quadrant that they fall in, we do not report the CI. However, *Appendix 2*, *Figure 8* presents the CEAC for the complete case analysis. At a cost-effectiveness threshold of £20,000 per additional live birth, there is a 11% probability that hysteroscopic resection represents the most cost-effective intervention and a 89% probability that the control group is most cost-effective. The probability of hysteroscopic resection representing the most cost-effective intervention increases to 38% at a cost-effectiveness threshold of £20,000 per additional live birth. This probability never rises above 42%, because the intervention was dominated by the control group in 58% of the bootstrap samples.

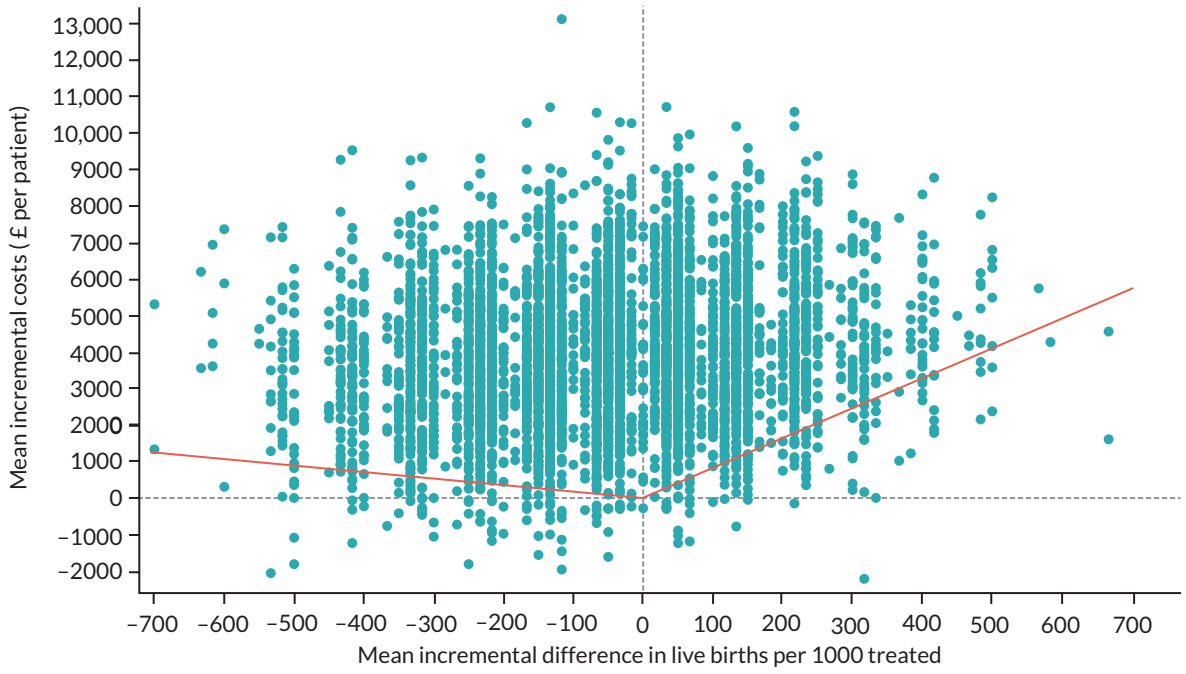



**FIGURE 7** Cost-effectiveness plane: incremental difference in costs and live births between the hysteroscopy group and the control group (5000 bootstrap replicates) – complete case analysis.

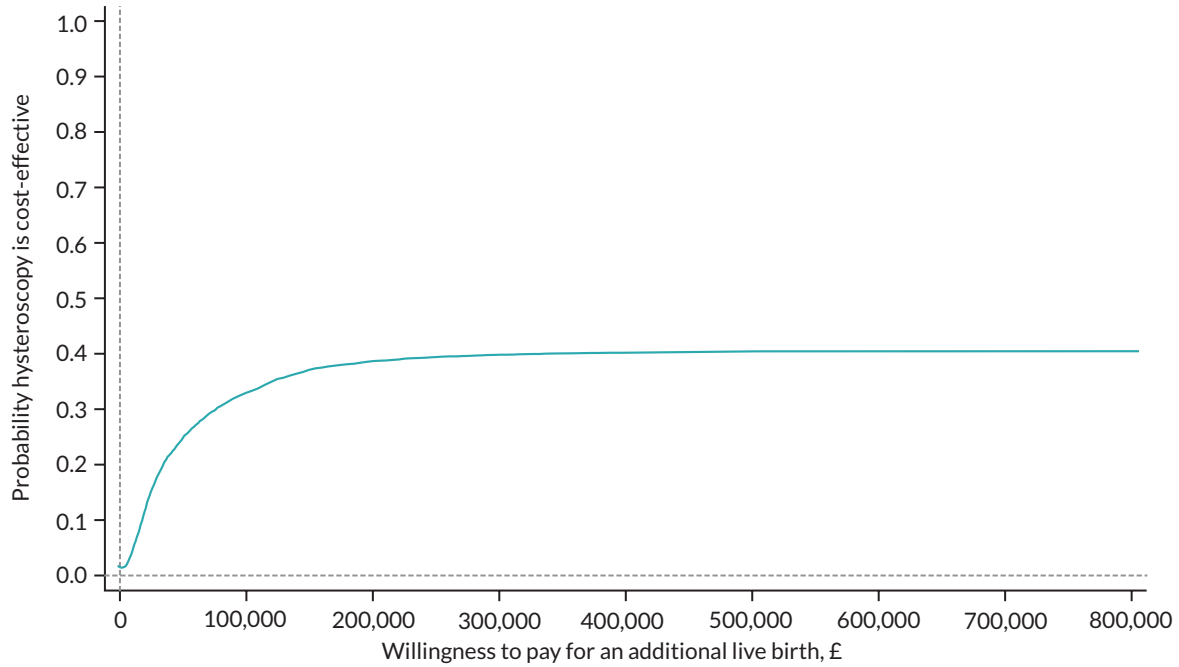



**FIGURE 8** Probability that hysteroscopy is cost-effective compared to the control treatment – complete case analysis.