**Title**

Induced endometrial trauma (endometrial scratch) in the mid-luteal menstrual cycle phase preceding first cycle IVF/ICSI versus usual IVF/ICSI therapy: study protocol for a randomised controlled trial.

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**Abstract**

**Introduction**

Endometrial Trauma commonly known as Endometrial Scratch (ES) has been shown to improve pregnancy rates in women undergoing In Vitro Fertilisation (IVF), with or without Intracytoplasmic Sperm Injection (ICSI), with a history of repeat implantation failure, however the procedure has not yet been fully explored in women having IVF/ICSI for the first time. This study aims to examine the effect of performing an ES in the midluteal phase prior to first time IVF/ICSI cycle, on the chances of achieving a clinical pregnancy and live birth. If ES can increase this success rate there would be a significant cost saving to the NHS through decreasing the number of IVF/ICSI cycles necessary to achieve a pregnancy, influence the practice of single embryo transfer (SET) and consequently have a large impact on risks/ costs associated with multiple pregnancies.

**Methods & Analysis**

This 30 month, UK, multi-centre, parallel group, randomised controlled trial including a 9 month internal pilot and health economic analysis recruiting 1044 women from 16 UK Fertility Units will follow up participants to identify if IVF has been successful and live birth has occurred up to 6 weeks post-partum. Primary analysis will be on an intention to treat basis. A sub-study of endometrial samples obtained during the ES will assess the role of immune factors in embryo implantation.

The intervention will perform an ES procedure in the mid luteal phase prior to first time IVF/ICSI treatment versus no intervention in the matching group, with 1:1 randomisation. The primary outcome is live birth rate (LBR) - after completed 24 weeks gestation.

**Ethics and dissemination**

The South Central – Berkshire NREC has approved the trial protocol. The findings will be submitted to peer- reviewed journals and abstracts will be submitted to relevant national and international conferences.

Trial Registration number: ISRCTN: 23800982

**Strengths and limitations of this study**

* This will be the largest randomised controlled trial to date performing an ES procedure in women having IVF/ICSI for the first time assessing the effectiveness and cost effectiveness of the procedure.
* The trial has the potential to inform the practice of offering this ‘add-on treatment’ as well as the practice of single embryo transfer.
* It will also determine whether performing an ES is an acceptable and well tolerated procedure.
* Due to the nature of the intervention it is not possible to blind study participants.
* Potential difficulty with recruitment if patients are not in equipoise about effectiveness of the ES procedure in first time cycles.

**Background**

The use of local endometrial trauma known as Endometrial Scratch (ES) to improve implantation rates in women undergoing assisted conception was first described in 2003 [1]. The procedure has since been explored in several studies mainly focusing on women with recurrent implantation failure and has been shown to significantly increase pregnancy rates by almost double [2–4]. Three recent systematic reviews have summarised the evidence, however each included different studies. A recent Cochrane review included fourteen randomised studies; seven in women with previous cycle failure, five in an unselected population and one in a first-time cycle [5]. The live birth rate meta-analysis combined trials regardless of the population (i.e. number of previous IVF cycles) and included five studies, reporting a risk ratio (RR) of 1.42 (1.08, 1.85), p=0.02 [6,7]. The odds of achieving a clinical pregnancy were also increased following ES with a RR of 1.34 (1.11, 1.62), p=0.002. The one trial conducted in women undergoing their first IVF cycle indicated the procedure was harmful with an OR of clinical pregnancy rate of 0.30 (0.14, 0.63) p=0.002 [8]. Notably, this trial performed the ES procedure at the time of oocyte retrieval and not in the month prior to the IVF cycle. Despite the concerns around the quality of evidence in using ES and that the trials undertaken so far have been small (most <150 participants), ES has been widely adopted into routine clinical practice in women with recurrent unsuccessful implantation and is currently being provided in units where women are having IVF/ICSI for the first time [9,10]. Therefore, it is essential that a large well controlled multi-centre trial is conducted to fully investigate the effectiveness and safety of this technique in women undergoing their first cycle of IVF.

The Human Fertilisation and Embryology Authority (HFEA) state in their statistical report into multiple births that the risks associated with multiple births is the single biggest health risk associated with fertility treatment [11]. Multiple births carry risks to the health of both the mother and the babies and that birth of a healthy singleton child, born at full term, is therefore the safest outcome of fertility treatment for both mother and child and is best achieved through promoting the practice of single embryo transfer (SET). Unfortunately, the HFEA recently removed the licencing condition to enable the enforcement of multiple pregnancy targets which is expected to lead to a potential decrease in the number of women having SET and consequently an increase in the multiple pregnancy rates.

Although SET may be associated with a slightly lower pregnancy rate in a single fresh IVF cycle, when a patient has a surplus of embryos generated during the treatment cycle and hence potentially more attempts at embryo replacement per cycle, the pregnancy rate is the same whether one or two embryos are replaced. Most strategies of SET are limited to women where there is a reasonable chance of having surplus embryos available for cryopreservation. If ES can improve the implantation potential of the embryo and therefore improve success rates, ES may encourage an expansion of current SET policies. Inclusion of women with a lower chance of having cryopreserved embryos and a more general increase in the implementation of the practice of SET, could consequently have a large impact on the risks and costs associated with multiple pregnancies as a result of IVF [12].

The exact mechanism by which ES may improve implantation is not yet known, however it is known that implantation is a complex process involving the release of a number of inflammatory mediators including uterine natural killer cells, leukaemia inhibitory factor and interleukin 15 [13]. It is possible that ES may lead to the release of inflammatory cells and mediators such as macrophages and dendritic cells, tumour necrosis factor-α, interleukin-15, growth-regulated oncogene-α and macrophage inflammatory protein 1B [14].

ES has also been shown to cause the modulation of several endometrial genes that may be involved in membrane stability during the process of implantation such as bladder transmembranal protein (UPIb) and adipose differentiation-related protein and mucin 1 [15].

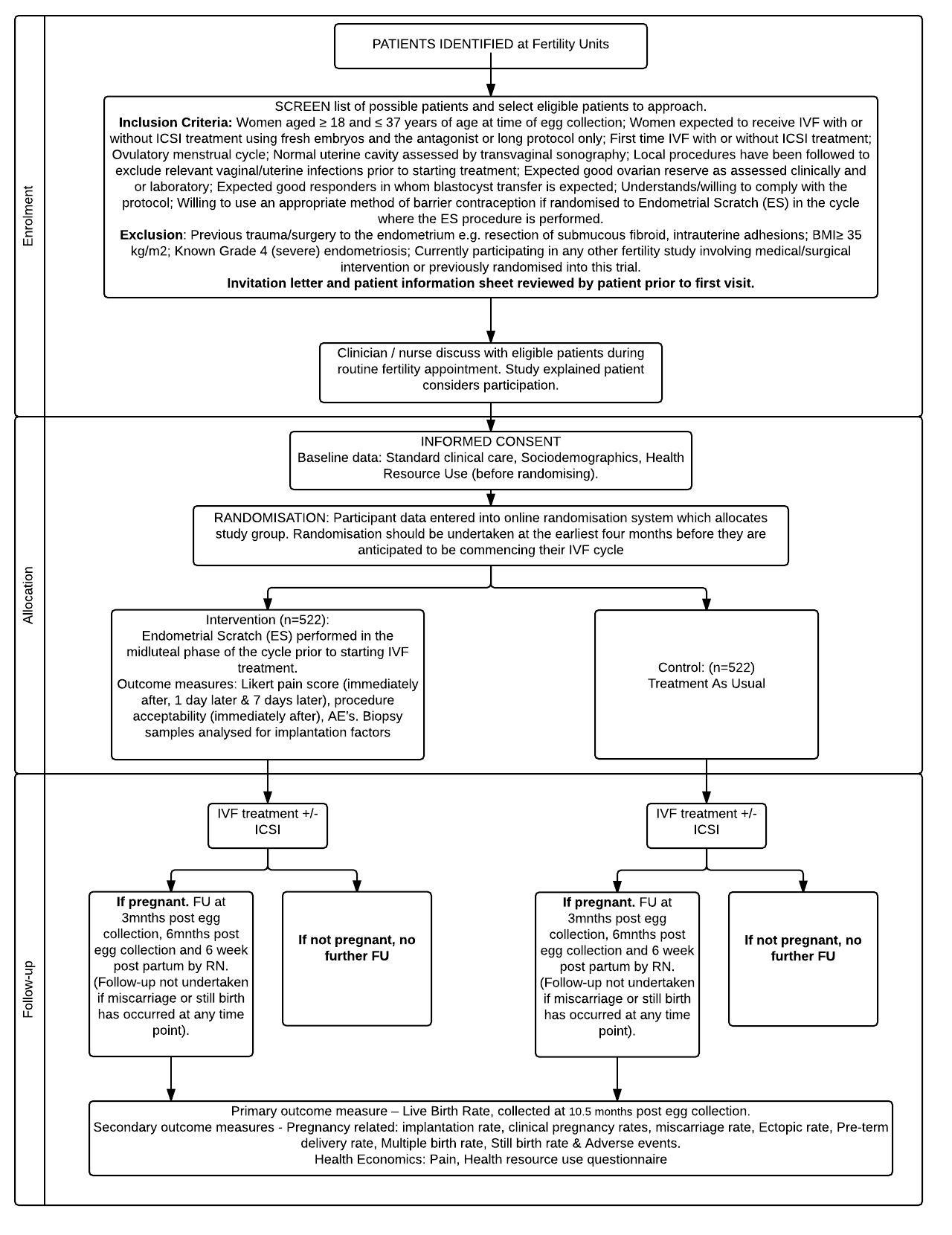
ES is routinely performed as an outpatient procedure. Risks have been identified in a previous study when the procedure was undertaken on the day of oocyte retrieval; however, the procedure is not known to be associated with any particular risks when undertaken in the menstrual cycle preceding that of IVF therapy, apart from period like discomfort whilst performing the procedure [8]. Taking simple analgesics prior to the procedure usually alleviates this. As with any intrauterine procedure there is a potential for intrauterine infection. However women attending for fertility treatment are usually screened for serious vaginal infections such as chlamydia to minimise the risk of any spread of infection when performing the embryo transfer procedure, a similar procedure to an ES as it involves the insertion of a catheter into the uterine cavity.

The main objectives of this trial are to assess the clinical and cost effectiveness of the ES procedure in women aged between 18 and 37 years (inclusive) undergoing their first IVF/ICSI cycle using either antagonist or long protocols to see if it could potentially improve implantation rates and hence encourage the practice of single embryo replacement. This could lead to a decrease in the multiple pregnancy rate associated with IVF treatment and the number of cycles needed to achieve a pregnancy. A sub-study will be undertaken in two of these centres (Sheffield and Southampton) where endometrial samples obtained from the ES procedure will be stored for later analysis into the role of immune factors in embryo implantation. The trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

**Method and Analysis**

The Endometrial Scratch Trial is a multi-centre, parallel group, randomised controlled trial to examine the clinical, cost effectiveness and safety of an ES performed in the mid-luteal phase prior to a first time In vitro Fertilisation cycle. Eligible participants will be randomised to either the treatment as usual (TAU) arm, consisting of usual IVF treatment, or the intervention arm where ES will be performed followed by usual IVF treatment. Two of the fertility units participating will obtain tissue from the endometrium at the time of the ES which will be analysed to identify endometrial factors that have a role in embryo implantation. The overall study design is illustrated below in the study flow chart (figure 1).

Figure 1. Study flow chart.



The trial consists of two phases - an internal pilot to assess feasibility of recruitment and delivery of the intervention, and a two year main recruitment phase.

The trial will commence with a 9 month internal pilot recruitment phase across approximately 6 sites to justify whether or not the recruitment strategy and the scheduling of the endometrial scratch procedure are feasible and will use the same trial procedures as described for the main trial.

At the end of the pilot phase, the Trial Steering Committee (TSC) will report to the funder on whether the feasibility criteria have been met and whether the trial should continue. Sheffield Clinical Trial Research Unit (CTRU) will aggregate feasibility of the research and intervention protocols based on the following outcomes.

The trial will be considered infeasible and will be stopped if either of the following conditions apply:

1. Feasibility of recruitment to the main trial: defined as recruitment of fewer than 108 participants (75% of the 144 target) during the internal pilot phase.

2. Scheduling of the ES procedure: defined as less than 75% of women scheduled to receive their ES procedure have received the ES at the correct time point.

**Recruitment**

Upon successful completion of the pilot the main trial aims to recruit women attending 16 UK Fertility Units for first time IVF treatment. Participation is entirely voluntary and choosing not to participate will not negatively influence the woman’s treatment in any way. Furthermore consent can be withdrawn at any stage. Women who are about to undergo their first cycle of IVF/ICSI will be identified by screening patients referred for IVF/ICSI treatment. Eligible women will be sent information regarding the study in the post or via e-mail. Women may also be alerted to the study via the study website or posters displayed at the fertility unit. If they are interested in participating they will be invited to discuss the trial with their fertility team at their next routine appointment.

Prior to randomisation fully written informed consent will be obtained by a suitably trained Doctor or Research Nurse/Midwife at a clinic visit. The participant will complete a study specific resource use questionnaire prior to randomisation to collect health care usage in the previous 3 months; baseline data will be collected at this visit and participants will be randomly allocated to either the intervention or usual care arm of the trial.

The trial is collaboration between research staff at The Jessop Wing, Sheffield Teaching Hospital NHS Foundation Trust & the University of Sheffield - Clinical Trials Research Unit who are responsible for the conduct of the trial. Funding to run the trial has been awarded by the National Institute of Healthy Research (NIHR) Health Technology Assessment (HTA).

Detailed methods of the Endometrial Scratch trial are described in the Endometrial Scratch protocol available on the website – <https://www.sheffield.ac.uk/scratchtrial>

Inclusion criteria

* Women will be included and considered suitable if aged between 18 and 37 years (inclusive) at the time of egg collection and having IVF/ICSI for the 1st time using the antagonist or long protocol only
* Are expected to receive treatment using fresh embryos and considered to be good responders to treatment ( Regular ovulatory menstrual cycle, Normal uterine cavity, expected good ovarian reserve) and where single embryo transfer is expected at the point of entry into the trial.
* Women will have no relevant vaginal/uterine infections and are willing to use an appropriate method of barrier contraception (if randomised to Endometrial Scratch in the cycle where the ES procedure is performed), understands and are willing to comply with the trial protocol.

Exlcusion criteria

* Women will be excluded if they have had previous trauma/surgery to the endometrium and have a BMI of 35 kg/m2 or greater with known grade 4 (severe) endometriosis, are currently participating in any other fertility study involving medical/surgical intervention.
* Are expected to receive ultra-long protocol, have previously received or have planned an endometrial scratch (or similar procedure, e.g. endometrial biopsy for the collection of Natural Killer Cells) or previously randomised into this trial.

**Sampling**

The primary outcome is the LBR. This is defined as a live birth after completed 24 weeks gestation within the 10.5 month or 6 week post egg collection-partum follow-up period. The denominator for calculating the LBR will be the number of women randomised to each group. Data from the HFEA suggests a Live Birth Rate of 32.8% in women under 35 and 27.3 % in women aged 35-37. The sample size calculation assumes a 30% LBR in the control group and that an absolute increase of 10%, to a 40% LBR (a relative risk of 1.33) in the intervention groups is of clinical and practical importance. The effect size, a 10% absolute difference in LBR, we are proposing is large but we believe an effect of such magnitude is needed to change clinical practice (there is a 5% absolute difference in LBR between women aged under 35 and 35-37) and is less than that observed in the systematic reviews described above (where the Relative Risk estimates ranged from 1.83 to 2.46). (where the Relative Risk estimates ranged from 1.83 to 2.29) [2,16].

To have a 90% power of detecting this difference or more, in LBR rates between the groups, as statistically significant at the 5% two-sided level, will require 496 women per group (992 in total). Adjusting for a predicted drop-out rate of 5% (due to anticipated difficulties of follow-up for patients who have been referred from NHS Trusts other than the participating Fertility Unit) we will require 1044 participants.

**Study procedures**

Following randomisation women in the intervention arm will have the ES procedure performed in the midluteal phase of their cycle prior to their planned IVF/ICSI cycle in the outpatient setting of the fertility unit. The choice of screening for infection prior to the procedure or the administration of antibiotics will be left to individual units according to their local established protocols and procedures. Women can be randomised any time up until they start their IVF cycle, although it may be necessary for the participant to delay her IVF if randomised to the intervention arm. This decision should be made and agreed by both the patient and her fertility team before randomisation is undertaken. Women will complete a visual pain scale (likert) to assess their pain and tolerability assessment of the procedure within 30 minutes of the initial ES procedure and then again at 24 hours and 7 days post procedure via an automated text message. Women Randomised to TAU will continue with their IVF/ICSI as planned and will not receive the ES procedure.

Following delivery of the ES, participants will undergo IVF in line with local procedures. Following successful embryo transfer (in both groups) a pregnancy test will be performed and adverse events will be collected. In women who do not undergo embryo transfer, the research team will make every effort to collect any adverse event information from either the patient or the medical notes. If a healthy pregnancy is confirmed the woman is discharged to normal antenatal care as per standard practice.

**Randomisation**

The randomisation schedule will be generated by Sheffield CTRU prior to the start of the trial and the randomisation sequence computer generated and stratified by site and protocol (antagonist or long protocol). Random permuted blocks of variable size will be used to ensure enough participants are allocated evenly to each arm of the trial at each site.

**Trial Intervention**

ES is a minor procedure of 10 to 20 minute duration that will be performed in an outpatient setting at local IVF centres in line with local procedures and the trial SOP. The participant will be required to use a barrier method of contraception (if necessary) during the menstrual cycle in which the ES will be performed. During ES, a speculum is inserted into the vagina and the cervix exposed and cleaned. A pipelle or similar endometrial sampler is then inserted into the cavity of the uterus; negative pressure is applied by withdrawal of the plunger. The sampler is rotated and withdrawn several times so that tissue appears in the transparent tube. The Sampler and speculum are then removed. If no tissue is seen in the transparent sampler, this is an indication that the sampler was not fully inside the uterine cavity and therefore the procedure is repeated.

Compliance to the intervention will be ascertained through the Clinician or Research Nurse/Midwife recording whether or not the patients has a) attended the clinic for the ES procedure and b) received the ES procedure as per protocol. Any deviation from the protocol will be noted and reported as per the Sheffield CTRU SOP.

**Follow-up**

Patient follow up will continue until the 1st cycle of IVF or the resulting pregnancy has concluded. If no pregnancy is confirmed the study is complete (regardless of which group the woman is randomised to). Pregnant women will be followed-up at 3 and 6 months post egg collection and then 6 weeks post-partum to collect pregnancy outcome data. If the pregnancy is ongoing at 3 months and 6 week post-partum, a health resource use questionnaire will be sent to the patient for completion. If a spontaneous pregnancy is achieved between randomisation and IVF treatment, the pregnancy will be followed up as per protocol.

If a woman achieves a spontaneous pregnancy following randomisation she will be followed up per protocol and included in the intention to treat analysis.

**Safety considerations, safety monitoring and AE reporting**

All AEs and Serious Adverse Events (SAE) will be recorded by the local research team at each Fertility Unit.

All SAEs and AEs will be followed up until satisfactory resolution or until the treating clinician and the principal investigator deems the event to be chronic or the participant to be stable.

Research Nurses/Midwives will ask patients for any details of adverse events at five time-points: post procedure (if randomised to receive ES), at the participants’ pregnancy test, and then, if pregnancy has been achieved, at 3 and 6 months post egg collection and finally 6 weeks post-partum.

SAEs and AEs will be collected up to the participants’ final study related follow-up event. If embryo transfer does not occur, the Research Nurse/Midwife will contact the participant approximately 2 weeks after egg collection to identify if any adverse events have occurred. In the case of a negative pregnancy test, the site research team should make every effort to obtain AE data from the patient or the medical notes at routine clinical care contacts; no further contact will be made outside of routine clinical care.

Expected AEs will be those which occur regularly due to pregnancy, and expected SAEs are those events which are expected in the patient population as a result of the routine care/treatment of a patient. Expected SAEs and all AEs will be collected as part of the trial and entered into the eCRF, but will not be reported to regulatory bodies (NHS REC/sponsor).

Unexpected SAEs will be reported to the Sheffield CTRU as soon as staff at the fertility unit becomes aware of the event.

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

**Outcomes**

The trial includes a health economic component to assess the cost of the intervention per extra live birth from an NHS and social care perspective. Resource use will include the intervention costs for ES, the cost of IVF treatment, visits to the assisted conception unit and for those who conceive antenatal and post-natal visits, delivery costs and any hospital stays not related to birth for both mother and baby. The resource use questionnaire will collect information on contacts with midwife and GP visits. A Patient Cost questionnaire will collect time taken to travel to appointments and loss of productivity. Unit costs will be derived from appropriate national sources and will include; NHS reference costs, Personal Social Service Research Unit costs and the **Office of National Statistics** [17–19]. The resource use questionnaire will be designed for this study and will draw on data collection tools developed in The School of Health and Related Research (ScHARR) and those collated by the Database for Instruments for Resource Use Measurement (DIRUM).

Primary clinical outcome

• Live birth rate; based on the number of live births after 24 weeks gestation within the 10.5 month (or 6 week post-partum) post egg collection follow-up period.

Secondary outcomes

• Acceptability and pain rating of the Endometrial Scratch procedure, a visual pain scale (likert) to assess their pain and tolerability assessment of the procedure within 30minutes of the initial ES procedure, 24hrs later and then again 7 days after the ES.

* Implantation rate
* Clinical pregnancy rate
* Miscarriage rate
* Ectopic pregnancy rate
* Multiple birth rate
* Preterm delivery rate
* Still birth rate
* Details of participant’s IVF cycle (fertilisation, egg collection and embryo quality & transfer)
* Adverse events
* Health resource use of the participant & patient costs

**Blinding**

Due to the nature of the intervention, it is not possible to blind patients or clinicians to treatment allocation. Since this trial evaluates objectively measured outcomes (pregnancy rates) that are unlikely to be affected by a placebo effect, it is not necessary to perform a sham procedure for the control group. The study statistician, Trial Steering Committee (TSC) and health economist will be blinded to allocation.

**Trial monitoring and oversight committees**

The trial will be overseen by the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC), membership of both will consist of independent experts in the field. The TSC will include a patient representative. Both committees will review recruitment, study progress and adverse events. The DMEC will receive monthly reports of recruitment and adverse events and, at their meetings, will also consider emerging evidence from other trials or research on ES. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about patient safety.

Day-to-day running of the trial will be coordinated by the Trial Management Group (TMG), consisting of the grant co-applicants, plus members of the Jessop Wing Fertility Unit, Sheffield CTRU and patient representatives.

**Statistical analysis**

Primary analysis will be performed on the intention to treat population (all participants randomised into the trial). All statistical exploratory tests will be two-tailed at 5% nominal level. Baseline demographic (e.g. age), physical measurements (e.g. BMI), and health-related data will be described and summarised overall and for both treatment groups. The women, not the IVF cycle will be the unit of analysis. If the woman fails to get pregnant or does not have IVF treatment, they will be included in the analysis of the primary outcome as a negative outcome (i.e. non-live birth). For sensitivity analyses, per protocol (PP) analyses will also be undertaken which will be defined as for Endometrial Scratch participants in the intervention group, receiving the ES procedure as documented in the study protocol and undergoing IVF/ICSI in the subsequent menstrual cycle, including embryo transfer. For the control group, the PP population will receive IVF/ICSI including embryo transfer. Sub-group analyses will be undertaken to explore the effect of important variables related to the participant and their treatment on the primary and secondary outcomes. These subgroups are:

• Day of embryo transfer (day 2, 3, 4, 5 or 6),

• Fertilisation method (IVF, IVF or ICSI, ICSI [spilt]),

• Type of protocol (long or antagonistic),

• Embryo transfer (single or double) and whether the embryo was fresh or frozen

• Previous history of consecutive miscarriages (0-2 vs >=3)

AEs will be reported as a proportion of all women randomised. Adverse events including serious adverse events will be compared between the two groups using a Fisher’s Exact test, Chi-squared test or negative binomial regression model in case of repeated events per woman (as appropriate). A 95% CI for the difference in adverse event rate between the groups will also be calculated with associated point estimate depending on the method used.

Health economic results will be presented in the net-benefit framework and will allow for uncertainty using bootstrapping and probabilistic sensitivity analysis.

**Ethics and dissemination**

The study is registered on the ISRCTN database (reference 23800982) and has been approved by the South Berkshire Research Ethics Committee (reference 16/SC/0151). The findings of this trial will be submitted to peer- reviewed journals and abstracts to national and international conferences. Other stakeholder specific outputs in relevant formats will also be produced for commissioners, IVF practitioners, third sector and user advocacy organisations. A website will be established to promote the work of the trial. All knowledge transfer activity including translation will be informed by input from trial collaborators, the TSC and TMG to ensure the study is meeting the needs of the commissioners and audience.

**Discussion**

This trial will determine whether performing an ES procedure prior to 1st time IVF/ICSI treatment is an inexpensive, safe and well tolerated procedure that increases the live birth rate in women having SET. If shown to be the case, this would have a significant improvement in first cycle IVF success rates and could potentially lead to significant cost savings to the NHS as fewer women would need to have repeat treatment cycles. This is particularly important in the current economic climate and with restrictions on funding and service provision. This would also have a significant impact for women, for whom the burden of repeated cycles is large.

**Acknowledgements**

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**Authors Contributions**

Contributors: MM, CP,YC, LM, JS, KB, JC,SW,TY, DP, SL,RC & MD conceived the study, and contributed to study design, sample size calculations and analytical plans. MM, CP, JC, & RC drafted the manuscript. MM, CP, YC, LM, JS, KB, JC, SW, TY, DP, SL, RC & MD initiated the project, have assisted in developing the protocol and helped with implementation. All authors read and approved the final manuscript.

**Competing interests**

None declared.

**Patient consent**

Obtained.

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