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A Multicentre Randomised Controlled Trial of Induced Endometrial Scratch in Women Undergoing First Time IN Vitro Fertilisation (IVF)

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Authorised by: Mostafa Metwally. Chief Investigator

Sheffield Clinical Trials Research Unit (CTRU)

A Multicentre Randomised Controlled Trial of Induced Endometrial Scratch in Women Undergoing First Time IN Vitro Fertilisation (IVF)

The Endometrial Scratch Trial

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

Contents

Abbreviations

ACU	Assisted Conception Unit
AE	Adverse Event
ES	Endometrial Scratch
DET	Double Embryo Transfers
eCRF	Electronic Case Report Form
ESHRE	European Society of Human Reproduction and Embryology
HFEA	Human Fertilisation and Embryology Authority
ICF	Informed Consent Form
ICSI	Intracytoplasmic Sperm Injection
IVF	In Vitro Fertilisation
PIS	Patient Information Sheet
PP	Per protocol
SAE	Serious Adverse Event
SET	Single Embryo Transfer
TAU	Treatment as Usual
FSH	Follicle-stimulating hormone
AMH	Anti-Mullerian Hormone

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Protocol amendments since Version 4

- Change of name of 10.5 months follow-up to 6 weeks post-partum.
- Clarification around how to follow-up participants who do not complete a full IVF cycle.
- Exclusion criteria added for participants undergoing protocols other than long or antagonist.
- Clarification that a participant should still remain in the trial (and follow-up carried out) if the intervention is not carried out.
- Detail added regarding collection of safety events at the time of pregnancy tests.
- Minor alterations made to list of sub group analyses.
- Conditions added to list of expected adverse events.
- Electronic questionnaire added at 3 month and 6 week post partum follow up.
- Summary letter introduced to be sent to participants who achieve a pregnancy in order to inform when the 3 telephone follow ups will be undertaken.

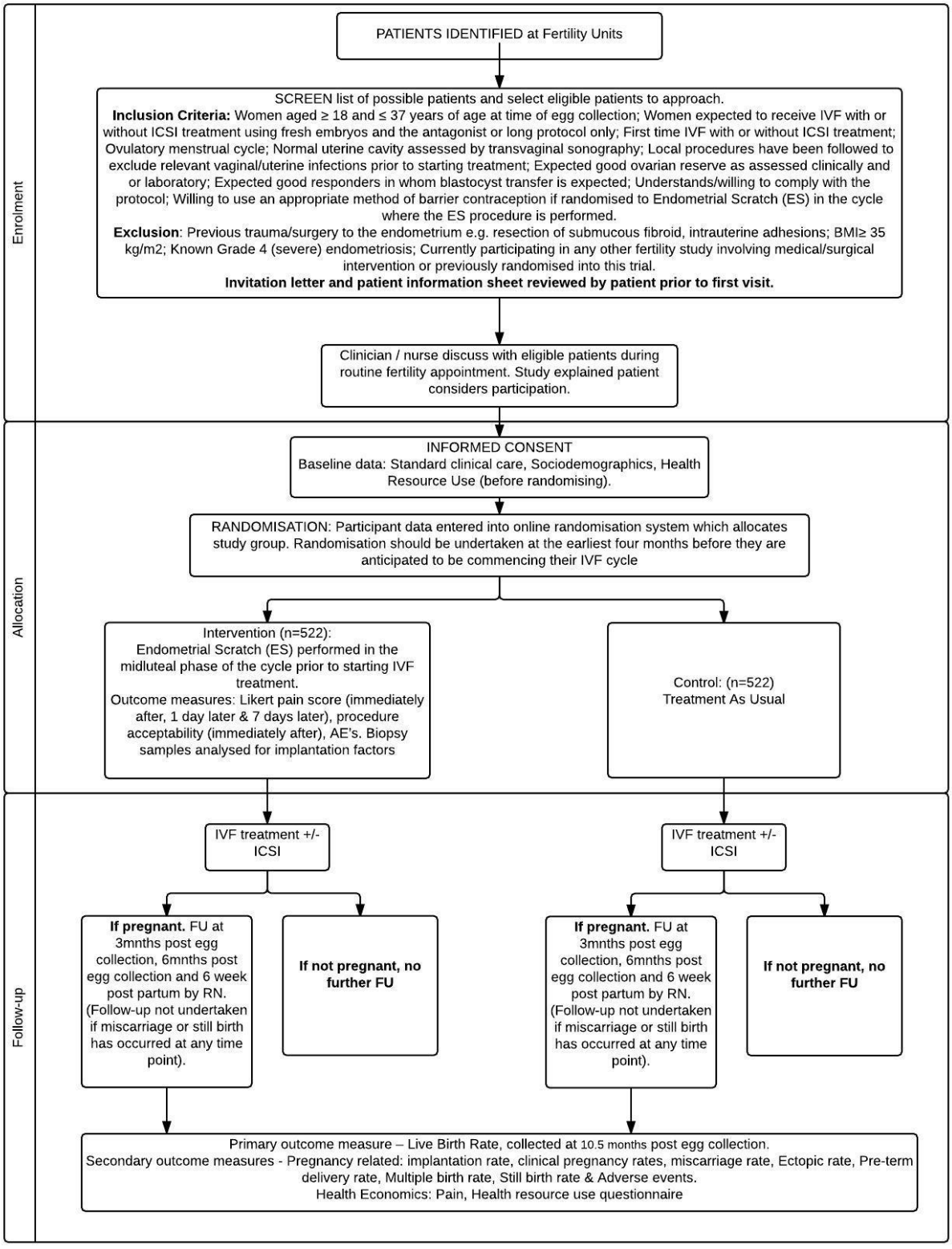
Trial Summary

Local Endometrial Trauma commonly known as Endometrial Scratch (ES) has been shown to improve pregnancy rates in women undergoing In Vitro Fertilisation (IVF) treatment, with or without Intracytoplasmic Sperm Injection (ICSI), with a history of repeat implantation failure. The procedure has not yet been fully explored in women having IVF/ICSI treatment for the first time. The study aims to examine the effect of an ES performed in the midluteal phase prior to a first time IVF/ICSI cycle, on the chances of achieving a clinical pregnancy and live birth.

This will be a multi-centre, parallel group, randomised controlled trial including a 6-month internal pilot recruitment phase to justify whether or not the recruitment is feasible. The trial will recruit 1044 women over 30 months (including the feasibility phase) from approximately 10 Fertility Units within the United Kingdom. Regardless of whether or not a participant is randomised to receive ES, she will be followed up to find out if IVF has been successful, and if so, if a live birth has occurred up to 6 week post-partum (figure 1). A sub-study will be undertaken at the Sheffield and Southampton sites, where consenting women randomised to the intervention arm will have a tissue sample of their womb analysed for endometrial factors that may affect the implantation rate.

If a beneficial effect is seen in women randomised to the intervention group, it would have a significant bearing on the success rate of IVF/ICSI treatment with a potential significant cost saving to the NHS through decreasing the number of IVF/ICSI cycles necessary to achieve a pregnancy. Through improving success rates, such a procedure could also have the potential to improve the implementation of the practice of single embryo transfer (SET), which would consequently have a large impact on the risks and costs associated with multiple pregnancies.

Figure 1: Patient flowchart



1. Introduction

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 since then has 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 only randomised evidence with five studies; three in women with previous cycle failure, one in an unselected population and one in first-time cycle [5]. The live birth rate meta-analysis included two studies and reported an odds ratio (OR) of 2.46 (1.28, 4.72), p=0.007 [6, 7]. The odds of achieving a clinical pregnancy were also over twice as likely after ES with an OR of 2.61 (1.71, 3.97), p<0.00001. However, conflicting evidence was provided by the trial by Karimzade (2010) indicating 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.

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 [9]. Multiple births carry risks to the health of both the mother and the babies.

The birth of a healthy singleton child, born at full term, is therefore the safest outcome of fertility treatment for both mother and child and this 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. This 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. Hence the rationale for encouraging SET. For this reason, most strategies of SET are limited to women where there is a reasonable chance of having surplus embryo available for cryopreservation.

By potentially improving the implantation potential of the embryo, ES may encourage an expansion of current Single Embryo Transfer policies to include women with a lower chance of having cryopreserved embryos.
Through improving success rates, such a procedure could have the potential to increase the uptake and implementation of the practice of single embryo transfer, which would consequently have a large impact on the risks and costs associated with multiple pregnancies which is the greatest risk of assisted conception treatment [10].

Despite the concerns around the quality of evidence in using ES and the fact that the trials undertaken so far have been very small (most <150 participants), ES has been widely adopted into routine clinical practice in women with recurrent unsuccessful implantation. It is therefore essential that a large well controlled multi-centre trial is conducted to fully investigate the usefulness and safety of this technique. The main objective of this study is to examine whether the use of ES in women undergoing a first IVF cycle could potentially improve implantation 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.
The exact mechanism by which ES may improve implantation is not yet know, 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 [11]. 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 [12].

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 [13].
ES is a routinely performed outpatient procedure. Risks have been identified in a previous study when the procedure was undertaken on the day of oocyte retrieval; 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 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.

The aim of this study is 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. A sub-study undertaken in the Sheffield and Southampton sites will assess the role of immune factors in embryo implantation. The trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

2. Aims and objectives

Aim

To examine the effect of an Endometrial Scratch (ES) performed in the midluteal phase prior to a first time In vitro Fertilisation (IVF) cycle (with or without ICSI), on the chances of achieving a clinical pregnancy and live birth.

Objectives

The main trial includes an internal pilot to determine the feasibility of recruiting patients to the trial and providing participants randomised to the intervention group with the ES procedure.

Internal pilot objectives:

I. The availability of eligible patients and the feasibility of participant recruitment to the main trial including the need to translate study material into other languages.

II. The feasibility of scheduling the additional procedure at the correct time in the treatment pathway.

Main trial objectives:

A multi-centre, parallel group, randomised controlled trial to examine the clinical effectiveness, cost effectiveness and safety of an ES performed in the midluteal phase prior to a first time In vitro Fertilisation cycle. The outcomes used to assess these objectives are described in section 8.

Since this trial evaluates objectively measured outcomes (pregnancy rates) that are unknown and unlikely to be affected by a placebo effect, it is not necessary to perform a sham procedure for the control group.

3. Trial Design

This study is a multi-centre, parallel group, individually randomised controlled trial comparing two intervention arms: Endometrial Scratch versus no Endometrial Scratch (i.e. Treatment As Usual (TAU)) performed in the midluteal phase prior to a first time IVF/ICSI cycle (undertaken using the antagonist or long protocols). Patients and clinicians will not be blinded to which arm of the study the participant is randomised to. The trial includes an internal pilot to assess operational feasibility objectives.

Pilot study

The trial will commence with a 9 month internal pilot recruitment phase across approximately 6 sites to justify whether or not the recruitment strategy is feasible.
We will assess the feasibility of the recruitment strategy and the scheduling of the endometrial scratch procedure. The pilot study will use the same trial procedures as described for the main trial (described later on in this protocol).

Feasibility outcomes

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

Main study

Following successful completion of the pilot study, the main trial will aim to recruit 1044 patients from approximately 13 Fertility Units across the UK over 30 months (including the pilot). The trial will recruit women referred for first time IVF treatment to receive either standard IVF treatment (control group) or IVF treatment with an ES (intervention group). They will then have their IVF treatment in the usual way as per standard procedure. The control group will have no intervention other than treatment as usual (TAU). Eligible women will be randomised to either of the two trial arms and followed up until 6 week post-partum (approximately 10.5 months post egg collection).

Economic analysis alongside this trial will be used to analyse the cost-effectiveness of ES versus treatment as usual and present results as the incremental cost per extra live birth.

Setting

Approximately 17 Fertility Units across the UK.

Population

The study aims to recruit women attending Fertility Units for first time IVF treatment. Potential participants will be identified by screening patients referred for IVF/ICSI treatment. Eligible women (who are eligible as per the criteria descried in section 5) 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 asked to talk to their fertility team at their next routine appointment.

The inclusion of willing participants will occur either at the time of the initial medical or nurse consultation at the participating Fertility Unit or at a later time during a routine fertility unit appointment, for example women who have been given information about the study at an earlier date and have expressed their interest to participate.

The doctor or nurse will emphasise that participation is entirely voluntary and that choosing not to participate will not negatively influence the woman's treatment in any way. Furthermore it will be emphasised that consent can be withdrawn at any stage.

Allocation

Following informed consent, women meeting the eligibility criteria will be allocated on ratio of 1:1 using stratified block randomisation with variable blinded block sizes. Stratification will be done by site and antagonist or long protocol. Eligible women will be allocated to either ES in the midluteal phase of the cycle prior to starting IVF treatment or Treatment as Usual. Randomisation will be done via a web-based randomisation system hosted by the Sheffield Clinical Trial Research Unit (CTRU).

Outcomes

Primary outcome

1. Live birth rate (LBR) - after completed 24 weeks gestation within the 10.5 months (or 6 weeks post-partum) post egg collection follow-up period.

Secondary outcomes

2. Acceptability of the Endometrial Scratch procedure, including pain rating and tolerability of the procedure directly after (or within 30minutes of the procedure), 1 day and 7 days post procedure of the procedure.
3. Implantation rate based on a positive serum Beta hCG on approximately day 14 following the egg collection or by a positive urine pregnancy test.
4. Clinical pregnancy rate; an observation of viable intrauterine pregnancy with a positive heart pulsation seen on ultrasound at/after 8 weeks gestation
5. Miscarriage rate as measured by spontaneous pregnancy loss (including pregnancy of unknown location (PUL) prior to 24 weeks gestation within the 10.5 month post egg collection follow-up period
6. Ectopic pregnancy as measured by the rate of pregnancy outside the normal uterine cavity
7. Multiple birth rate, defined as the birth of more than one living foetus after completed 24 weeks gestation
8. Preterm delivery rate as measured by live birth after 24 weeks before 37 weeks gestation within the 10.5 month post egg collection follow-up period.
9. Still birth rate based on the delivery of a still born foetus showing no signs of life after 24 weeks gestation within the 10.5 month post egg collection follow-up period.

10. Details of participant's IVF cycles including number of eggs retrieved, number of embryos generated 1 day after egg collection, quality of the embryos transferred (using NEQAS grading) and the number of embryos replaced and day of embryo replacement.

Safety outcomes

11. Adverse events (refer to section 8).

Health Economics

12. Health resource use of the participant measured at baseline, 3 and 10.5 months (or 6 weeks post-partum) post egg collection.
13. Patient costs at 3 months post egg collection.

Design measures to avoid bias

The primary outcome is a "hard-endpoint", thus reducing bias.

The Trial Steering Committee (TSC), the study statisticians and health economists will be blinded to treatment allocation whilst the trial is ongoing, but the Trial Manager, Trial Support Officer and participants will not be blinded. Analysis will be by intention-to-treat (ITT). The Data Monitoring and Ethics Committee (DMEC) will also be blinded, with the ability to unblind if necessary. Participants cannot be blinded due to the nature of the intervention. Trial staff, apart from the trial statisticians and health economist, will not be blinded to treatment.

Where individuals are lost to follow-up or data is missing, imputation methods will be employed, which will be described in the statistical analysis plan.

Data Source

Data will be sourced directly from the patient and medical notes and entered into a secure online database hosted by Sheffield CTRU. Every effort should be made at each participating centre to enter data directly into the trial electronic case report form (eCRF). Stored patient information will be pseudo-anonymised - names and addresses removed and a unique study identifier added, with the exception of consent documentation.

4. Ancillary sub-studies

Sheffield and Southampton Tissue Sub-Study

A tissue sub-study will be undertaken to identify endometrial factors that have a role in embryo implantation. Participants recruited in the Sheffield and Southampton sites will have the opportunity to consent to participate in a sub-study, which will be led and analysed by Dr Susan Laird at Sheffield Hallam University, Mostafa Metwally at Sheffield Teaching Hospitals and Ying Cheong at Southampton University. Consent for this sub-study will be sought at the same time as consent into the main trial. Participants will be able to participate in the main trial without consenting to participate in this sub-study, but not vice-versa.

Endometrial tissue will be obtained from consenting women at the time of their ES procedure. Obtaining this tissue will not require an extra procedure, nor will it add additional discomfort; the tissue will be harvested from the Pipelle sampler that is inserted into the uterus to undertake the scratch procedure. Samples will be collected and stored in specimen pots containing formalin within the Sheffield and Southampton Fertility Units.

The tissue sample obtained will then be stored in liquid nitrogen for up to 10 years at Sheffield Hallam University and Southampton University under the supervision or Dr Susan Laird and Dr Ying Cheong. The tissue samples will be anonymised and coded prior to storage and the liquid nitrogen dewers in which they will be stored will be kept locked. Samples may be transferred off-site for analysis. If so, samples will remain anonymous and will be transported in accordance with the Human Tissue Authority Code of Practice.

The amounts of various immune factors such as leucocytes, cytokines, and adhesion molecules will be determined using quantitative PCR to measure mRNA levels and Immunocytochemistry and Western Blotting to determine protein levels. This work will not involve investigation of genetic biomarkers.

The outcomes measured will be the amounts of the specific immune factor mRNA or protein, or number of cells. The levels of expression or cell number will be related to pregnancy outcome. The absolute amounts will be compared in women who have a successful pregnancy and those who do not using ANOVA and the student t-test or

the Mann Whitney non-parametric test if the data is not normally distributed. If 100 patients are recruited to the sub-study about 30% would be expected to have a successful pregnancy, which would be approximately 30 women. Previous studies support the use of this sample size, which will be large enough to detect differences between the two groups of women [11, 14, 15]. This will enable us to determine whether these endometrial factors play a role in the embryo implantation process.

5. Selection and withdrawal of participants

Inclusion/Exclusion Criteria

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

Inclusion

1. Women expected to be aged between 18 and 37 years (inclusive) at time of egg collection.
2. First time IVF with or without ICSI treatment using the antagonist or long protocol only
3. Expected to receive treatment using fresh embryos.
4. Expected good responders to treatment, with:

    a. Ovulatory menstrual cycle (Regular menstrual cycles defined by clinical judgement or with ovulatory levels of midluteal serum progesterone as defined by local laboratory protocols)
    b. Normal uterine cavity (assessed by transvaginal sonography at screening and no endometrial abnormalities such as , suspected intrauterine adhesions, uterine septa, submucosal fibroids or intramural fibroids exceeding 4 cm in diameter as assessed by the investigator that would require treatment to facilitate pregnancy).
    c. Expected good ovarian reserve (assessed clinically, biochemically (FSH< 10 & normal follicular phase oestradiol levels and or normal AMH), and or sonographically (antral follicle counts) and no history of previous radiotherapy or chemotherapy). [All laboratory/ultrasound standards based on local normal reference ranges.]
    d. Single embryo transfer (SET) expected.

5. Local procedures have been / will be followed to exclude relevant vaginal/uterine infections prior to starting treatment.

6. Willing to use an appropriate method of barrier contraception if randomised to Endometrial Scratch (ES) in the cycle where the ES procedure is performed. .
7. Understands/willing to comply with the protocol.

Exclusion

1. Previous trauma/surgery to the endometrium (e.g. resection of submucous fibroid, intrauterine adhesions.)
2. BMI of 35 kg/m2 or greater
3. Known grade 4 (severe) endometriosis
4. Currently participating in any other fertility study involving medical/surgical intervention
5. Expected to receive protocols other than antagonist or long (e.g. ultra-long protocol)
6. An endometrial scratch (or similar procedure, e.g. endometrial biopsy for the collection of Natural Killer Cells) is planned
7. Previously randomised into this trial

Consent

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

Participants will be provided with the study Participant Information Sheet (PIS) prior to consenting ***(documents: Sheffield and Southampton PIS, Generic PIS)***. Patients will then be required to provide informed, written consent ***(documents: Sheffield and Southampton Consent Form, Generic Consent Form)***. It is not foreseen that participants will be lacking in physical or mental capacity to provide informed consent, as such individuals would not be eligible to receive IVF treatment. Consent will be sought to inform the participant's GP of her involvement in the study ***(document: GP Letter)***.

Where the patient has the capacity to provide informed consent but is unable to sign or otherwise mark the consent form, we will follow the same procedure which the clinic adopts for such cases in regards to signing HFEA consent forms for assisted conception treatment, as specified by the HFEA:

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

If a translator is needed, the study team will endeavour to make available the provision of a translator service in the spoken language of the participant per standard local NHS Trust arrangement. The right of the patient to refuse consent without giving reasons will be respected. Furthermore, the participant will remain free to withdraw from the study at any time without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be recorded in the participants' hospital notes. The original consent will be filed in the hospital notes, a copy retained in the investigator site file and a second copy will be given to the participants. With the participants' consent their GPs will be notified using the REC approved GP letter provided. Once consent has been obtained, the participants details will be recorded on the trial enrolment log.

The associated risks of the ES procedure are fully documented on the REC approved Patient Information Sheet (PIS). However, if any further safety information which may result in significant changes to the risk/benefit analysis is identified, the PIS and informed consent form (ICF) will be reviewed and approved accordingly. All participants who are yet to receive the intervention will be informed of the updated information and given a revised copy of the PIS to sign, confirming their wish to continue in the study.

As with most multi-centre RCTs, there is variability in local procedures across all centres. All clinical elements of IVF/ICSI treatment, apart from the randomised interventions, will be carried out according to local protocols.

Recruitment

Figure 2 describes the recruitment process, which will be undertaken as follows:

1. Potentially eligible women will be recruited into the study via one of the following routes:

   a) women will receive a letter of invitation introducing the study (in the post, or by email) and a copy of the patient information sheet or the joint summary patient information sheet ***(document: Joint Patient Information Sheet)*** with their clinic appointment letter **(*documents: Patient Invitation Letter; Email Invitation; Joint Patient Invitation Letter; Joint Email Invitation)***.

   b) patient information sheets and/or the joint summary patient information sheet may be distributed to women attending an introductory patient information session which occurs at some units before their first consultation;

   c) women who have been informed about the trial via the website, recruitment film (based on the participant information sheet) or a poster ***(document: poster)*** will be advised to discuss the study with their clinician;

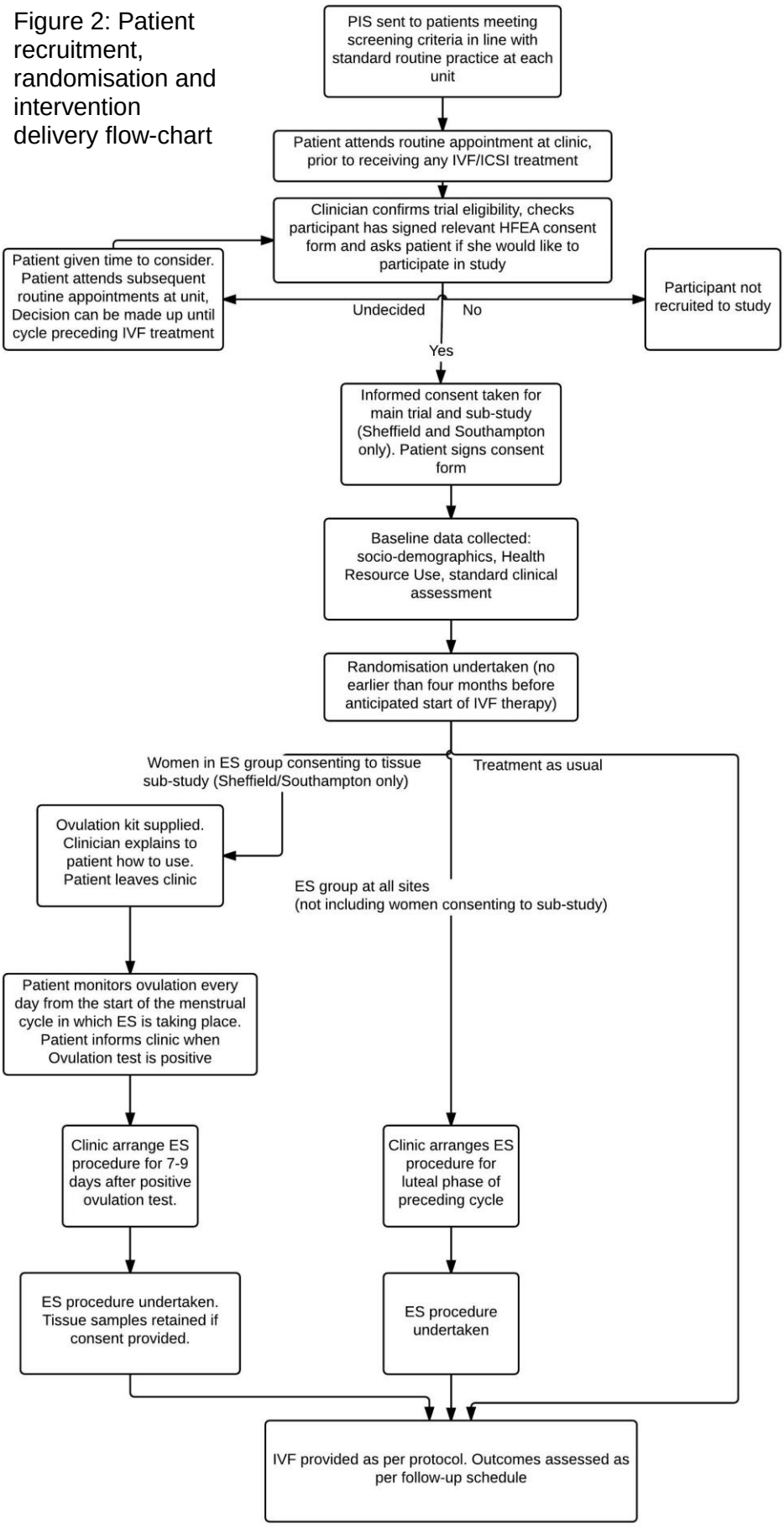
   Participants may be recruited at any stage prior to commencing their IVF/ICSI treatment cycle, via a letter or email or by the participant being approached by a member of their fertility team.

   Regardless of which method is used to approach women, they may be contacted by the Research Nurse (via email, telephone or text message) to ask if they are interested in participating in the study (***document: Recruitment Reminder Text)***. The Research Nurse will attempt to contact the participant up to approximately two weeks after the woman has first been alerted to the study via any of the methods outlined above. The Research Nurse will ask the potential participant if she has any questions related to involvement in the study. The Research Nurse will either a) confirm with the participant the date/time of their next routine visit, and confirm that consent will be sought on that day, or b) if the woman is not interested in participating in the study, will confirm that the participant will not be contacted again.

2. Eligible women will be invited to participate and will be given as much time as required, up until the start of their IVF treatment to ask questions about the study and discuss their participation with their clinician/research nurse or clinic nurse.

3. Following consent, baseline data including health & wellbeing questionnaires must be collected prior to randomisation. If consent is refused or if the patient is not eligible then the reasons for refusal/ineligibility will be requested, basic information will be recorded to enable completion of CONSORT diagram.

Figure 2: Patient recruitment, randomisation and intervention delivery flow-chart



Criteria for withdrawal

Patients may request to withdraw from the study at any time. Study data will be retained up to the point of withdrawal. If any of the exclusion criteria are identified at any stage of the trial, or if the woman does not undergo IVF as planned, the participant will remain in the study and will not be withdrawn. Details will be recorded to allow discussion about inclusion in the per protocol analysis. Patients who proceed to have a double embryo transfer will not be excluded from the study but the number of embryos transferred will be taken into account during the final analysis

6. Randomisation and Enrolment

Randomisation and allocation concealment

The Sheffield Clinical Trials Research Unit (CTRU) will oversee randomisation. A member of the local research team will log in to the web-based randomisation system and will enter the participant's details and will then be allocated a participant identification number. Details entered onto the system will include confirmation of signed consent, study site, age and treatment protocol. Randomisation should therefore only be undertaken once the patient's treatment protocol has been decided – this may be decided after informed consent is obtained; randomisation may therefore need to be undertaken at a subsequent routine appointment.

Randomisation should be undertaken no earlier than four months before the participant is due to commence her IVF therapy (see figure 3). 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.

Participants will then be randomly allocated to either the intervention or usual care arm of the trial. The clinician will make a note of this in the patient's medical notes.

If a woman achieves a spontaneous pregnancy following randomisation she will be followed up as per protocol procedures in accordance with the intention to treat analysis.

The randomisation schedule will be generated by the CTRU prior to the start of the trial. The randomisation sequence will be computer generated and stratified by site

and protocol (antagonist or long). 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.

Regardless of which group the participant is randomised to, the participant's GP will also be notified of their involvement in the study if consent is obtained to do so ***(document: GP Letter).***

7. Trial treatment

The Endometrial Scratch will only be provided to women who are randomised to the intervention arm of the trial.
ES is a minor procedure performed in daily clinical practice in an outpatient setting as per local procedure.
The participant will be required to use a barrier method of contraception (if necessary) in the cycle where the ES will be performed. Before ES is undertaken participants will be asked if they had complied with this. A speculum will be inserted into the vagina and the cervix exposed and cleaned. A Pipelle or similar endometrial sampler (as per local procedures) is then inserted into the cavity of the uterus; negative pressure is applied by withdrawal of the plunger. The sampler is then rotated and withdrawn several times so that tissue appears in the transparent tube. The Sampler and speculum are then removed. In total the ES procedure takes approximately 10 to 20 minutes. 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 can be repeated.

Scheduling treatment

Women who are randomised to receive ES will receive the ES procedure in the mid-luteal phase of the preceding cycle (figure 3). Women will contact the clinic when their menstrual cycle begins. Women who fail to contact the site will be telephoned by the Research Nurse. The ES procedure will then be scheduled for the mid-luteal phase as per local protocol. A letter will be sent to the participant to confirm the appointment ***(document: Procedure Appointment Letter)***.

NOTE: Women who have consented to participate in the tissue sub-study at the Sheffield site and randomised to receive the ES procedure will be supplied with an ovulation kit at their routine clinical appointment in which they consent to participate

in the trial. The women will inform the Fertility Unit when the test is positive (LH surge has been detected). ES will be performed 7-9 days later.

If a participant does not receive ES as planned before their first IVF cycle, the ES can be rearranged for the next menstrual cycle, which may require IVF to be delayed. This decision will be made at the discretion of the participant and her fertility team. If applicable, women should be made aware of this requirement before consenting to participate in the study. If ES is not received for any reason, then the participant should still be followed-up as required in the study procedures unless consent is withdrawn.

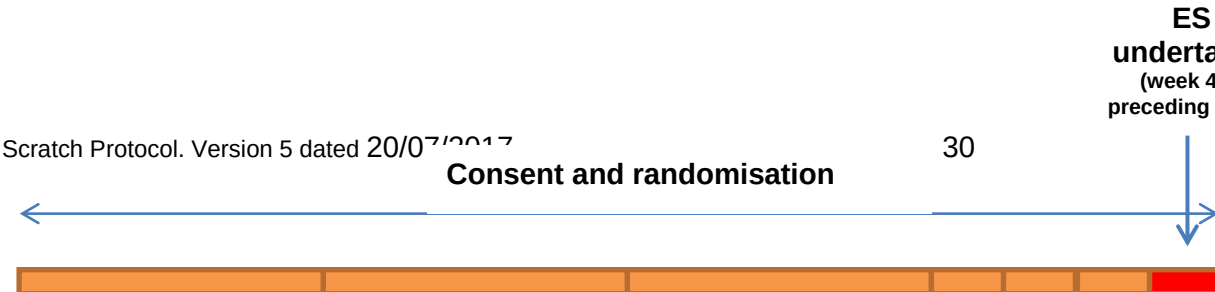
IVF treatment following the Endometrial Scratch

Following ES, no further interventions will be performed above normal care. Routine IVF treatment commences with the start of the woman's next menstrual bleed in line with local protocols using the Antagonist or Long Protocols only.

If embryo transfer is not undertaken for any reason in the first IVF cycle then in order to collect all Adverse Event information the researcher will continue to contact the patient approximately 2 weeks after egg collection.

If a participant commences stimulation but does not complete IVF for any reason then for the purposes of this trial, the women is classed as having received her first cycle of IVF and therefore her involvement in the trial is complete. Pregnancies obtained from frozen embryo transfer (FET) will be followed up on a case by case basis. The local trial research team should contact the Lead Research Nurse to clarify follow up procedures for these participants.

Figure 3: Consent, randomisation and ES procedure time-line



Compliance

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

Allowed medications

Any medication which is perceived as being allowed during an IVF cycle is permitted.

8. Assessments and procedures

Data items

Data will be collected at the following time points (See table 1 below):

Primary clinical outcome

1. Live birth rate- based on the number of live births after 24 weeks gestation within the 10.5 month post egg collection follow-up period. The denominator for calculating the LBR will be the number of women randomised to each group. In the event of multiple live births per mother (e.g. twins or triplets etc.), these will be counted as only one live birth for the numerator.

Secondary outcomes

2. Acceptability of the Endometrial Scratch procedure, including pain rating and tolerability of the procedure directly after (or within 30minutes of the procedure), 1 day and 7 days post procedure of the procedure.
3. Implantation rate based on a positive serum Beta hCG on approximately day 14 following the egg collection or by a positive urine pregnancy test.
4. Clinical pregnancy rate; an observation of viable intrauterine pregnancy with a positive heart pulsation seen on ultrasound at/after 8 weeks gestation
5. Miscarriage rate as measured by spontaneous pregnancy loss (including pregnancy of unknown location (PUL) prior to 24 weeks gestation within the 10.5 month post egg collection follow-up period
6. Ectopic pregnancy as measured by the rate of pregnancy outside the normal uterine cavity
7. Multiple birth rate, defined as the birth of more than one living foetus after completed 24 weeks gestation

8. Preterm delivery rate as measured by live birth after 24 weeks before 37 weeks gestation within the 10.5 month post egg collection follow-up period.
9. Still birth rate based on the delivery of a still born foetus showing no signs of life after 24 weeks gestation within the 10.5 month post egg collection follow-up period.
10. Details of participant's IVF cycles including number of eggs retrieved, number of embryos generated 1 day after egg collection, quality of the embryos transferred (using NEQAS grading) and the number of embryos replaced and day of embryo replacement.
11. Adverse events (refer to section 8).
12. Health resource use of the participant measured at baseline, 3 and 10.5 months post egg collection (or 6 weeks post-partum).
13. Patient costs at 3 months post egg collection.

NOTE: The Research Nurse/Midwife will not contact the women if the cycle has not achieved a pregnancy or the pregnancy no longer continues.

Study Procedures

Consent and randomisation

• Following consent and prior to randomisation baseline data including health & wellbeing questionnaires will be collected. The woman will then be randomised into the intervention arm or treatment as usual (TAU) using an online randomisation system. Women should be randomised into the study no earlier than four months before they are anticipated to be commencing their IVF therapy (see figure 3). Women can be randomised any time up until they start their IVF therapy, 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.

NOTE: The ES procedure should be performed in the cycle prior to their planned IVF cycle.

• Once randomised to the study those women randomised to receive the Endometrial Scratch procedure will contact their clinic when their menstrual cycle begins and arrange to have the ES procedure performed in the mid-luteal phase of that cycle as per local protocols.

- If clinically indicated the participant will be required to use a barrier method of contraception in the cycle where the Endometrial Scratch will be performed. If the woman was required to use a barrier method of contraception but contraception cannot be confirmed prior to the procedure being received then the procedure should be delayed until the next cycle, but this should be discussed with the patient and clinical team as it will result in a delay of the IVF treatment. If the woman does not wish to delay her IVF treatment then she should continue with her IVF/ICSI as planned without receiving the ES procedure. A non-compliance form should be completed and they will be excluded from the per-protocol analysis.

Intervention delivery

- Women will be advised to take a suitable analgesic prior to the ES procedure for pain relief.
- Woman will be asked to complete 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.
- Routine IVF/ICSI commences
- Women Randomised to 'Treatment as Usual' (No ES procedure) will continue with their IVF/ICSI as planned and will NOT receive the ES procedure.
- Following successful embryo transfer (in both groups) a pregnancy test will be performed in line with local procedures. Depending on the level of the pregnancy hormone (BhCG) the test may need to be repeated again in 48 hours. Adverse events will also be collected.
- In women who do not undergo embryo transfer, the research nurse will telephone the participant at a similar time point to collect adverse events.
- In cases of positive pregnancy and If a healthy pregnancy is identified the woman is discharged to normal antenatal care.
- If no pregnancy is confirmed the study is complete (regardless of which group the woman is randomised to).

Data collection Up to 8 weeks post egg collection

At routine care visits after a pregnancy has been confirmed the research nurse/midwife will contact the patient and review the medical notes to collect the following outcome data:

1. Implantation & clinical pregnancy information
2. Ectopic pregnancy information
3. Miscarriage information

4. Adverse event information

Note: When contacting the patient via the telephone a standard proforma will be used to standardise the collection of information across all units.

Follow-up

3 months (approximately 12 weeks gestation) post egg collection (if pregnancy has occurred)

The research nurse/midwife will contact the patient to:

1. Confirm the pregnancy is ongoing or if miscarriage has occurred.
2. Collect Adverse Events information
3. If miscarriage has occurred the study is now complete

Health and social care resource use questionnaire and patient costs questionnaire sent from CTRU if pregnancy continues.

6 months (24 weeks gestation) post egg collection (if pregnancy is still ongoing)

The research nurse/midwife will contact the patient to:

1. Collect miscarriage, still birth or pre-term birth information.
2. Collect Adverse Events information.
3. If miscarriage/still birth or pre-term birth has occurred the study is now complete

6 week post-partum(if pregnancy is still ongoing)

The research nurse/midwife will contact the patient to:

1. Collect Live birth or multiple birth information or still birth or pre-term birth information.
2. Collect Adverse Events information.

Health and social care resource use questionnaire sent from CTRU if a live birth or pre-term live has occurred.

Study is now complete.

	Baseline	Day of ES procedure, 1 day after ES and approx. 7days after ES (intervention arm only)	During routine care visits to fertility unit (approx. 8 weeks post-egg collection) prior to referral to antenatal care	Routine pregnancy test (or at a similar time point if embryo transfer not undertaken)	3 months (approx. 12wks gestation) post egg collection (if pregnancy has occurred)	6 months (approx. 24wks gestation) post egg collection (if pregnancy is still ongoing)	6 week post-partum (if pregnancy is still ongoing)	Method
Demographics	□							Patient self-reports to clinician
Standard clinical assessment	□							Patient self-reports to clinician
Pain assessment of ES		□						Patient self-reports to clinician via text/email
Live birth rate							□	Telephone contact with RN
Implantation rate			□					RN review of medical notes
Clinical pregnancy rate				□				RN review of medical notes
Ectopic pregnancy rate			□	□				RN review of medical notes
Miscarriage rate			□		□	□		RN review of medical notes (up to 8 weeks) and telephone contact with RN (3 months)
Pre-term delivery						□	□	Telephone contact with RN or via medical notes
Multiple birth rate							□	Telephone contact with RN or via medical notes
Still birth rate						□	□	Telephone contact with RN or via medical notes
Health and social care resource use questionnaire	□				□		□	In person questionnaire (baseline), questionnaire sent by post by Sheffield (CTRU) (3 months post egg collection and 6 week post-partum)
Patient Costs Questionnaire					□			Questionnaire sent by post by Sheffield (CTRU)
Adverse Events and Serious Adverse Events		□*	□*	□	□	□	□	Note review, contact with participant at routine visit and telephone contact by RN

Table 1: Outcome assessments

* Adverse events collected if RN is made aware via routine patient contact;

;ACU= Fertility Unit; ES= Endometrial Scratch; RN= Research Nurse

Method of data collection

Assessments will involve the following procedures, as described in figure 3:

1) Collection of baseline characteristics at the individual's routine IVF consultation ***(document: [Baseline] Resource Use).*** Data will be collected prior to randomisation, including sociodemographic variables, as well as a standard clinical assessment.
2) For those women randomised to the ES procedure:
    a. Collection of pain rating within 30 minutes of the procedure using a Likert scale ***(document: [Post procedure] Likert Pain Scale)***. The clinician/research nurse/clinic nurse undertaking the procedure will collect this from the participant and enter this information into the online database as soon as possible. The woman will also be asked about the tolerability of the procedure at this time point.
    b. Collection of pain rating 1 day ***(document: [1 day] Likert Pain Scale)*** and 7 days ***(document: [7 days] Likert Pain Scale)*** after procedure. The patient will be sent a text message (or email) to assess their pain score using a Likert scale***.*** If they fail to complete the pain score at either time point, they will receive a reminder text and/or email using the same text as the initial text. If no response is received after the reminder, participants may be contacted again via text message, telephone or email to obtain their pain rating.
3) For all women, regardless of which arm of the trial they are randomised to:

    Following egg collection, study participants will be followed up at their routine IVF appointments within the fertility unit. In order to identify participants, Research Nurses will keep track of when participants are visiting the unit, and access their notes after each visit, in order to determine if implantation pregnancy ectopic pregnancy or miscarriage has occurred. At the participants' routine pregnancy test, the Research Nurse will make every effort to collect any adverse event information from either the patient or the medical notes. Adverse events will also be collected at routine clinic appointments preceding the routine pregnancy test, if the fertility team is made aware of any.
4) Once pregnancy has been confirmed, patients will be contacted by the Research Nurse via telephone at 3, 6 and 6 week post-partum to identify the status of the pregnancy. Telephone contact with the patient will be prompted by a pro-forma ***(document: Telephone Follow-up Pro-forma)***. If a

pregnancy has been achieved (after consent and prior to ES/IVF commences) via a method other than IVF (i.e. spontaneously), the pregnancy will be logged, and follow-up will be undertaken as described. The Research Nurse will send a letter to the participant to clarify when the three telephone follow ups will be due ***(document: Email or Letter Reminder for Telephone Follow-ups).*** If the patient is not contactable at the first telephone call, the woman will be contacted until contact is made. A reminder email or text may be sent to the participant also ***(document: Follow-up Text).*** If the RN cannot get in contact with the patient after one week, a letter ***(document: Follow-up Letter)*** will be sent, or email (using the same text) if preferable, to ask the patient to contact the RN. Every effort will be made by the local research team to obtain end point data from other members of the multi-disciplinary team i.e., obstetrics and gynaecology. If the pregnancy has ended pre-term and did not result in a live birth (i.e. miscarriage, still birth), the patient will not be sent the questionnaires, and her involvement in the study will end. A card will be sent to the participant documenting the support services available to her and thanking her for her participation in the study ***(document: Support Letter)***

At the 3- and 6 weeks post partum time points, Sheffield CTRU will send questionnaires (with a covering letter) to the patient containing the Health Resource Use Questionnaire ***(document: Cover Letter for Questionnaires, [3 month] Resource Use, [6 week post-partum] Resource Use)*** only after the Research Nurse has confirmed that the pregnancy has progressed as normal (i.e. miscarriage or still birth has not occurred). At the 3 month time point a Patient Costs Questionnaire will also be sent to the patient ***(document: [3 month] Patient Cost Questionnaire).*** At both time points, the questionnaire may be sent via post, electronically (via email) or both via post and electronically ***(document: Cover Letter for Questionnaires, Cover Letter or Email for Electronic Questionnaires).*** If a participant does not return/complete their questionnaire within approximately one to two weeks, the participant will be contacted via text message, letter or email to ask her to return/complete the questionnaire ***(document: Text & Email Reminder to Complete Questionnaires, Reminder Letter for Questionnaires)***. If an electronic version of the questionnaire has not already been sent to the participant, it may be sent at this point. If the questionnaire is not returned following this, the CTRU or site research nurse will contact the participant by

telephone. If a pre-term live birth is identified at the 6 week post-partum phone call, the questionnaire will still be sent to the participant.

5) Following completion of follow-up at 6 week post-partum (, the patient will have concluded her involvement in the study. If a woman is pregnant at this point, and the pregnancy has not yet concluded, RNs may wish to follow-up the patient after the 12 month time point if or when information regarding the outcome of the pregnancy is known via routinely collected data by the Fertility Unit (such data is routinely collected as per HFEA legislation).

Ethical considerations to be taken into account when following up patients at 3-, 6 and 6 week post-partum

It is important that telephone calls to find out how participant's pregnancy is progressing are handled sensitively.

The HFEA requires the Fertility Unit that provided the IVF treatment to follow-up the outcome of all pregnancies. This means that women who take part in the trial will be contacting their Fertility Unit if miscarriage, still birth, pre-term delivery or full-term delivery occurs. Each unit will have different methods of contacting women to remind them to do this. For the majority of participants, we will know prior to contacting them at 3-, 6- or 6 week post-partum if the pregnancy has not continued to full term. In which case, patients will be contacted (to obtain adverse event data, but questionnaires will not be sent out), but the member of the site research team will contact them knowing that the pregnancy is not continuing and be able to communicate appropriately. Women may forget to inform the Fertility Unit of such an event occurring, in which case research sites will unfortunately be contacting them following the loss of their pregnancy, without knowing as such.

The site Research Nurse (or an active member of the research team who is familiar with the participant) should make contact at the 3-, 6- and 6 week post-partum follow up time points. As per usual practice, counselling or referral to another service should be offered if required. This situation should be handled with the upmost sensitivity and will commence with a discussion about how the woman has been since she last had contact with a member of the research team and then progress onto discussions about the pregnancy. Every effort should be made to ensure that each telephone contact is made by the same person to ensure continuity. The quality of life questionnaires will only be sent from the Clinical Trials Unit once it is established from the site Research Team that the pregnancy is continuing.

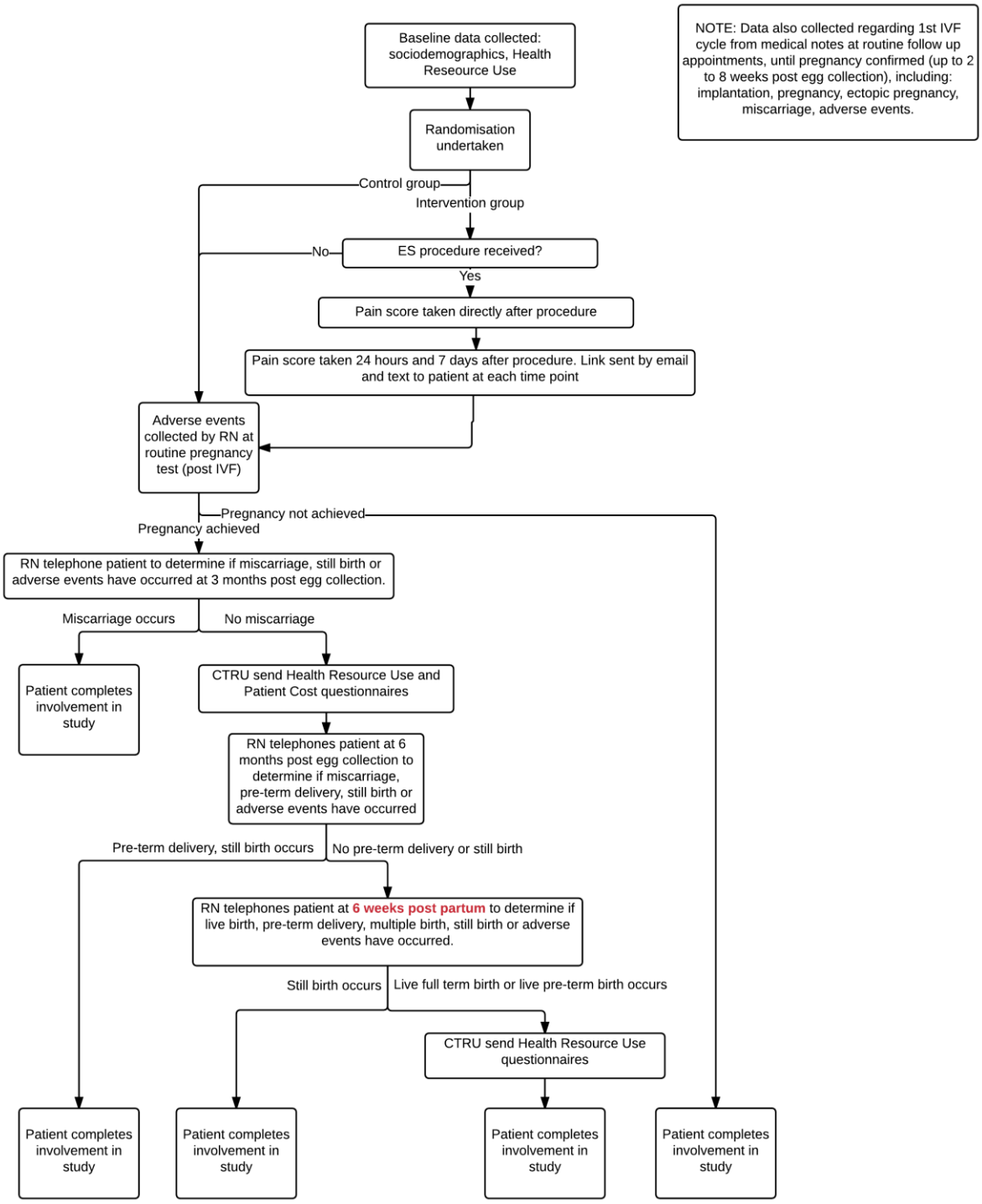


Figure 3: Outcome assessment flowchart

Adverse Events (AE) and Serious Adverse Events (SAEs)

An Adverse event (AE) is defined as any untoward medical occurrence in a participant, which does not necessarily have to have a causal relationship with this intervention.

The study will record Adverse Events (AE's) and Serious Adverse Events (SAEs) in both the Endometrial Scratch and treatment as usual groups. Any potential side effects of the ES procedure will be collected.
The trial will not be recording expected adverse events in this known patient population. Please refer to appendix 1 for a comprehensive list of expected adverse events.

Collection of Adverse Events and Serious Adverse Events

Adverse Events

Research Nurses 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 & 6 months post egg collection and finally 6 weeks post-partum follow-up. At the time of the pregnancy test, In the case of a negative 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.

. AEs that are not classed as expected in women who achieve pregnancy (documented in appendix 1) will be recorded on the CRF. AEs will be collected up to the participants' final study related follow-up event. If embryo transfer does not occur, the Research Nurse will contact the participant approximately 2 weeks after egg collection to identify if any adverse events have occurred.

Serious Adverse Events

The site PI (or Research Nurse, if this task is delegated to them by the PI) will decide if an adverse event should be classed as serious, using the following definition:

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires participant hospitalisation or prolongation of existing hospitalisation
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

AEs or SAEs may also be identified by the Research Nurse, or any other individual, at any point during the study and should be reported if required as outlined above.

Expected Serious Adverse Events

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

It is possible that during their pregnancy, participants will be admitted to hospital for treatment or monitoring of their pregnancy. Therefore expected SAE's will include hospitalisations for the following events:

Events related to the pregnancy/IVF therapy

Routine treatment or monitoring of miscarriage, ectopic pregnancy or threatened preterm birth, not associated with any deterioration in condition including:

- Premature Rupture Of Membranes or suspected PROM

Treatment which was elective or pre-planned for a pre-existing condition that is unrelated to the indication under study and did not worsen including:

- Elective Caesarean Section

Admission to a hospital or other institution for general care not associated with any deterioration in condition including:

- Hospitalisation for rest
- Hospitalisation for observation or monitoring of pregnancy
- Hospitalisation for maternal discomfort
- Hyperemesis
- Ovarian Hyperstimulation Syndrome (OHSS)
- Hypertensive Disorders of pregnancy
- Antepartum haemorrhage
- Gestational Diabetes (GDM)

- Post-partum haemorrhage
- Placenta Praevia
- Accreta Placenta
- Placental Abruption

Events relating to the baby when born:

- Low birth weight
- Very low birth weight
- Large for gestational age
- Preterm delivery
- Very preterm delivery
- Small for gestational age

Unexpected Serious Adverse Events

An unexpected SAE is any event that meets the definition of an SAE and is not detailed in the list above as expected. The following SAE's must be reported:

- Maternal death
- Stillbirth
- Congenital anomaly detected antenatally or postnatally (Common minor congenital anomalies as defined by the EUROCAT minor anomaly exclusion list will not be included as unexpected Serious Adverse Events. These excluded anomalies are either minor (e.g. skin tags), or expected for the gestation (e.g. patent ductus arteriosus in babies born <37 weeks).
- Neonatal death (up to 6 weeks post-partum)
- Any other event that is not foreseeable and meets the requirement of an SAE

Unexpected SAEs will be reported to the Sheffield CTRU as soon as staff at the research site becomes aware of the event. Still birth, congenital anomalies and neonatal deaths will be reported using the study database. For other events, details will be recorded on a SAE form (filed in the Investigator site file or downloaded from the AE eCRF page) and the form e-mailed to the Sheffield CTRU. If this is not possible, the unexpected SAE may be reported by telephone and the SAE form completed by staff at the Sheffield CTRU. Follow-up or corrections to information should be reported on a new SAE form and forwarded to the CTRU in Sheffield. Sheffield CTRU will be responsible for reporting SAEs to the sponsor and the REC.

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

9. Statistics

Sample size

The primary outcome is the live birth rate (LBR). This is defined as a live birth after completed 24 weeks gestation within the 6 week post-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 (where the Relative Risk estimates ranged from 1.83 to 2.29) [2, 5].

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.

Data analysis

Quantitative analysis

Routine trial monitoring

At approximately 12 to 18 month after the first patient is randomised, the time difference between randomisation and commencement of IVF will be assessed in randomised patients in order to assess the impact of these delays on the collection of the primary outcome. If, for instance, a significant number of patients have their IVF delayed, it will result in the primary outcome (live birth) not occurring within the follow-up timescale (6 week post-partum), which may require changes to the protocol and follow-up schedule.

End of study analyses

Statistical methods: As the trial is a pragmatic parallel group individual randomised RCT, data will be reported and presented according to the latest CONSORT guidelines. Primary statistical analyses will be performed on an ITT basis. 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. Under the ITT principle women will be included in the ITT analysis once they are randomised as per allocated treatment. If the women fail to get pregnant or do not have IVF treatment, they will be included in the analysis of the primary outcome as negative outcome (i.e. non-live birth).

The primary outcome is the live birth rate (LBR).This is defined as the birth of a living baby after completed 24 weeks gestation 6 weeks post-partum follow-up period. The denominator for calculating the LBR will be the number of women randomised to each group.

Our analysis will be a pure ITT analysis. There are several potential issues that will be dealt with as follows:

1) Before the commencement of IVF treatment, a small number of participants randomised to receive the ES procedure may not have received it. In this scenario, we will attempt to rearrange the ES for the next cycle. Women who are randomised to ES but do not receive it and go on to receive their IVF will be analysed in the ES arm.

2) Women who do not receive their IVF cycle in either arm will be included and analysed as a treatment failure in their allocated treatment arm.

3) Ideally, after 5 days, eggs fertilised in vitro develop into blastocyst and a single blastocyst is transferred. There will be some women (in both arms) that will not have sufficient high quality embryos to proceed to the blastocyst stage. These women will have eggs developed to embryos and after 2-3days will have double embryo transfer rather than blastocyst transfer. These women will be included in the ITT and analysed as per treatment allocated. This should be minimised due to the age group we have selected for the

study i.e. those women most likely to be good candidates for single embryo transfer.

4) Women who become spontaneously pregnant will be included and analysed according to treatment allocation.

The ITT population (and safety) populations will consist of all women who consent and are randomised to receive ES or TAU.

For sensitivity analyses, per protocol (PP) analyses will also be undertaken which exclude the women from the above scenarios. The PP population is defined as, for 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.

The primary binary outcome, the live-birth rate (LBR), will be compared between the two groups (ES and treatment as usual (TAU)) using a Chi-squared test. A 95% confidence interval (CI) for the difference in LBR between the groups will also be calculated. In the event of differences between the ES and TAU groups with respect to baseline demographic, physical, and health-related quality of life measurements, multiple logistic regression will be used to adjust the treatment effect for these variables. The maximum likelihood estimated adjusted regression coefficient estimate (the OR for live birth in the ES treatment group compared to the TAU group) for the treatment group parameter along with its 95% CI will then be reported.

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, ICSI, ICSI [spilt]),
- Type of protocol (long or antagonistic),
- Embryo transfer (single or double)
- Whether the embryo was fresh or frozen
- Previous history of consecutive miscarriages (0-2 vs >=3)

Secondary binary outcomes such as the multiple birth rate, implantation rate, clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate, pre-term delivery rate and still birth rate will be analysed in a similar way to the primary outcome.

We will report AEs as a proportion of all women randomised. Adverse events including serious adverse events (death; hospitalization (initial or prolonged); disability or permanent damage; other important medical events), will be compared between the two groups (ES treatment and treatment as usual (TAU)) 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.
We shall also repeat the above analyses on the PP.

An exploratory sub-group analysis using multiple logistic regression, with the primary outcome LBR, will look for an interaction between treatment group (ES or TAU) and sub-groups defined by a) those undergoing standard IVF and those undergoing ICSI treatment and b) those receiving long protocol and antagonist protocol IVF therapy.

For the primary outcome, LBR, any missing birth outcome data, which is only likely to occur if the mother moves away, will be imputed through a "best" case (i.e. assume the woman had a successful live birth) and "worst" case scenario (i.e. assume the woman had an unsuccessful pregnancy) and the results compared with the available data analysis.

Detailed statistical methods for all outcomes and scenarios will be described in a related trial Statistical Analysis Plan.

Health economic analysis

The primary analysis will present results as cost per extra live birth from an NHS and social care perspective in accordance with NICE guidelines [16].Women will be asked to complete a questionnaire to collect their resource use at baseline, 3 months post egg collection and 6 weeks post-partum. . 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 sent at 3 months post egg collection 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 ScHARR and those collated by the Database for Instruments for Resource Use Measurement (DIRUM).

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

10. Trial supervision

Trial Steering Committee (TSC)

The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. At least 75% of its member should be independent, and it should include an independent chair and a patient representative. The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

The TSC provides independent supervision for the trial, providing advice to the chief investigator and the Sponsor on all aspects of the trial by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials. If the Chief Investigator and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all other associated with the study, may write through the Trial office to the Chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

Trial Management Group (TMG)

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

The core TMG will consist of:

- Chief Investigator
- Project Manager
- Clinical Trial Co-ordinator
- Data Manager
- Trial Statistician

- Patient representative(s)

The core TMG will meet regularly at least once every two months, but rising to at least once per month before key milestones (ethical approval, recruitment initiation etc.).

In addition, investigator meetings will be set up during the recruitment phase of the study, at least once every two months, where the site PIs (or another delegated individual) will discuss pertinent issues with the research team, including recruitment, data completion and intervention delivery.

Data Monitoring and Ethics Committee (DMEC)

The DMEC will meet prior to TSC meetings, in order to inform the TSC of data and safety issues.

They 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. DMEC meeting will be held every 6 months, the first after recruitment has commenced.

11. Data handling and record keeping

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

Patients will be allocated a unique identification number that will be used to identify them throughout the trial. All data collection forms, except those collecting demographic or contact details, will be anonymised and will contain the unique patient identifier.

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

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

Data stored on a computer (i.e. information inputted in an electronic eCRF) will be stored on a secure database, accessible on the internet, which adheres to data protection and NHS regulations.

Identifiable data, including names, addresses and dates of birth, will be shared with Sheffield CTRU. Consent will be obtained from the patient for this to occur.

12. Data access and quality assurance

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from CTRU (study manager, research assistant and data managers), the sponsor and host organisations to permit study related monitoring, audits and inspections. Select CTRU staff will have access to personal data including names, addresses, phone numbers and email addresses in order to undertake the questionnaire follow-up. In addition to this, access to the eCRF and questionnaire data will be required for study monitoring and audit purposes. A study monitoring plan will be devised in accordance with the Sheffield CTRU SOPs on Trial Monitoring (QU001) and Data Management Plan (DM009).

The study database resides on Sheffield CTRU's in house data management system. The system uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the study sponsor. All paper documents will be stored securely and kept in compliance with the Data Protection Act (1998). Data entered onto the eCRF's will be automatically transferred for storage in an electronic database hosted by CTRU on behalf of the sponsors in which the participant will be identified only by a study specific number. The participant's name and any other

identifying details will be stored in the database held by CTRU on behalf of the sponsor. After the trial has been completed and the reports published, the data will be stored in a secure physical or electronic location with controlled access.

Monitoring Plan

The CTRU QA manager has conducted a risk assessment of the study and determined the potential risk as low risk. The nature, frequency and intensity of trial monitoring will be outlined in the trial monitoring plan as determined by the CTRU risk assessment. The monitoring plan will explain what will be monitored, which/what proportion of data fields and who will be responsible for conducting the monitoring visits, and who will be responsible for ensuring that monitoring findings are addressed. Investigators and their hosts Trusts will be required to permit trial-related monitoring and audits, providing direct access to source data and documents as requested. Trial participants will be made aware of the possibility of external audit of the data they provide in the participant information. A random selection of consent forms and source data from each centre may be sent via email or post to Sheffield CTRU for monitoring purposes. Both will be sent in a secure manner.

13. Publication

The trial protocol will be published on an open access source. A number of academic outputs will be produced as the data is analysed throughout the trial. Journals will be selected based on the highest possible impact.

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.

14. Finance

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

15. Ethics approval

Ethical approval (IRAS) and R&D approvals will be obtained before any recruitment starts. It can be a difficult period emotionally undergoing IVF. Endometrial scratch is already used in routine clinical practice for other clinical indications (e.g. abnormal uterine bleeding etc), it is also currently used by many units after multiple failed IVF cycles but it is not currently used in the first IVF/ICSI cycle. Therefore, we do not anticipate any significant ethical issues with the use of an already widely used procedure. However, given its potential benefit, women may feel disappointed should they be randomised to the control arm of the trial. As such, the information that will be provided verbally and through an information sheet, which will be developed in consultation with patients and representatives of the patient involvement group, will be designed to ensure that it is presented in a sensitive way whilst explaining the nature of the trials randomised design. The information sheet clearly explains the participation in the trial is voluntary with the option of withdrawing at any stage and the participation or non-participation will not affect their usual care. Only Individuals who are NHS employees (substantive or honorary) and who have access permissions will examine hospital databases for potentially eligible participants.

The approval letter from the ethics committee and a copy of the approved patient information / consent form must be sent to the CTRU before initiation of the study (for each site).

Monitoring is the responsibility of Sheffield CTRU and will be performed at the beginning, middle and end of the study in line with SOP's.

Ethical Considerations

The protocol and any subsequent amendments along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee (REC). Written approval from the Committee must be obtained and subsequently submitted to the local R&D department to obtain final R&D approval.

Participation Record Retention & Archiving

During the course of the research all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 5 years. The sponsor or sponsors

representative will hold responsibility for record retention and archiving to relevant procedures. Archiving of the site files and participants' records at each participating centre will be the responsibility of the local R&D department. Funding will be provided for this.

Protocol compliance

The CI will ensure that the trial is conducted in compliance with the protocol, principles of the Declaration of Helsinki (1996) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework (2005), Good Clinical Practice Guidelines (1996), Trust & Research Office policies and procedures and any subsequent amendments.

Protocol non-Compliance

Definition: 'A noted systematic lack of both the CI and the study staff adhering to Declaration of Helsinki (1996) applicable regulatory requirements but not limited to the Research governance Framework, GCP, Sponsor's and Sponsors' delegated representatives' policies and procedures and any subsequent amendments, which leads to prolonged collection of deviations, breaches or suspected fraud.'

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communication and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are dealt with accordingly, the R&D office will agree an appropriate action, including an on-site audit.

Trial Organisation and Responsibilities

To ensure the smooth running of the trial and to minimise the overall procedural workload it is proposed that each participating centre should delegate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professional to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research and for reporting any failure in these respects, adverse events or suspected misconduct through the appropriate systems.

Local Coordinator at each centre

Each centre will have a local Principal Investigator who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. Close collaboration between all clinical teams is particularly important in ES in order that patients for whom ES is an option can be identified sufficiently early for participation.

The local PI should ensure that all medical, nursing and midwifery staff involved in the care of infertility services are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

Nursing or Midwifery Coordinator at each site

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

Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Research Governance Framework 2005. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support the main REC, site specific assessment and R&D submissions, clinical set-up, ongoing management including training, monitoring reports and promotion of the trial.

The CTRU trial manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D approval has been obtained.

The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

The CTRU will develop the trial monitoring plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of non-compliance.

16. Regulatory approval

The study will be registered with, and approval gained, from all relevant regulators, including the South Central-Berkshire Research Ethics Committee. Local R&D approvals, from each participating NHS trust, will also be sought.

17. Indemnity / Compensation / Insurance

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96 (48) will operate in this case. However, it should be stressed that in term of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

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19. Appendix 1.

The following is a list of AE's related to pregnancy that are expected in this patient population.
Abdominal pain
Anaemia
Clicky hip
Cholecystitis
Conjunctivitis
Constipation
Cough
Diarrhoea
Dizziness
Epistaxis
Facial pain
Fall
Gestational diabetes
Headache
Hypertension
Itchy skin
Nausea
Vomiting
Palpitations
Pelvic girdle pain
Possible fetal abnormality
Pre-eclampsia
Proteinuria
PV bleed
PV discharge
Rash
Reduced fetal movement
Spontaneous labour 36W
Strep B infection
Symphysis pubis disorder
Urinary tract infection
Vaginal infection
Viral infection