AE/SAE Reporting Protocol

1. Purpose

This guideline describes the procedure for identifying, recording, managing and reporting adverse events (AEs) and serious adverse events (SAEs) that occur in participants of the Endometrial Scratch trial. This document summarises the procedures outlined in the Sheffield Clinical Trials Research Unit Standard Operating Procedure for Adverse Events and Serious Adverse Events (PM004 V2.0) and must therefore be used in conjunction with this SOP.

2. Background

Participants are recruited into the Endometrial Scratch (ES) trial from fertility unit databases or hear about the trial via the website or posters in the units. Trial participants will be randomly allocated to either receive the endometrial scratch intervention or usual care, and will be followed-up during their routine IVF treatment, and then at 3-, 6- and 10.5 months (or 6 weeks post partum) after egg collection (if they become pregnant). AEs and SAEs will be collected that are related to the study participant. SAEs, including congenital abnormalities and neonatal death, will be collected for the neonate also (up to 6 weeks post-partum).

3. Reporting time points

AEs and SAEs will be collected at the following time-points:

- Directly after the ES procedure (ES group only)
- Routine pregnancy test (ES and usual care groups)
- 3-, 6- and 10.5 months (or 6 weeks post-partum) post egg collection (ES and usual care groups)

Note 1: if a participant does not undergo a pregnancy test (due to egg collection or embryo transfer not occurring), AEs will be collected via the research nurse telephoning the participant approximately two weeks after when egg collection or embryo transfer should of occurred.
Note 2: participants will only be followed up if they become pregnant and until a live birth/miscarriage/still birth occurs.

4. Responsibilities

4.1. Site trial staff is responsible for recording unexpected AEs and all SAEs using the SAE Report Form (Appendix 2) and making them known to the study PI.

4.2. The PI is responsible for assessing serious adverse events for their relatedness to the study and reporting all serious adverse events to the Clinical Trials Research Unit (CTRU) in Sheffield.

4.3. The CI/CTRU is responsible for reporting to the Sponsor/Trial Steering Committee and REC within 15 days of notification if the event is deemed to be related to the trial. If the PI is unable to assess the SAE for any reason, the CTRU will arrange for the CI to undertake this assessment. The report form for notifying NRES can be found in Appendix 3 or on the HRA website (http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/)

5. Definition of AEs and SAEs

5.1. adverse event

Any untoward medical occurrence that is not expected in a participant (that does not necessarily have to have a causal relationship with the study)

For the purposes of the Endometrial Scratch trial, adverse events do not include "expected" outcomes or events that occur during the course of the IVF cycle, e.g. failed fertilisation, miscarriage, ectopic pregnancy and OHSS, unless such event meets the definition of a Serious Adverse Event (e.g. leads to hospitalisation) as this information is collected at other time points.
AEs that are related to the ES procedure e.g. dizziness, bleeding, discharge should be reported as an AE or an SAE if involving hospitalisation.

5.2. Serious adverse event

Any adverse event that:

- *results in death*
- *is life-threatening[(a)] (subject at immediate risk of death)*
- *requires hospitalisation or prolongation of existing hospitalisation[(b)]*
- *results in persistent or significant disability or incapacity.*

or is a congenital anomaly/birth defect

For the purposes of the Endometrial Scratch trial, serious adverse events also include neonatal deaths, occurring within 6 weeks post-partum.

(a) 'life-threatening' in the definition of 'serious adverse event' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(b) Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

(c) Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious,

6. Reporting of Adverse Events

An overview of the process can be found in Figure.1

6.1. Adverse events

Expected adverse events (see Appendix 1- this list applies to events during pregnancy) will be documented on an ongoing basis in the electronic case report form (eCRF)

Unexpected adverse events which are not listed in appendix 1 and therefore not expected during pregnancy will be entered into the eCRF (see appendix 2 for data collection form).

6.2. Serious adverse events related to the mother

1. When an event is identified the local PI should be notified immediately who will assess the event for expectedness and classification as an SAE. An SAE Report form (see Appendix 2) should then be completed and emailed or faxed to the Sheffield CTRU within 24 hours of the SAE being identified. If the PI is unavailable then the form should be completed as fully as possible and sent to the CTRU, where the CI will assess expectedness and classification.

Fax: Completed SAE report forms to the CTRU Fax 0114 222 0870. The account will be checked during office hours (between 9am and 5pm Monday to Friday).

Email: Completed forms should be emailed to ctru-saes-group@sheffield.ac.uk. The email account will be checked during office hours (between 9am and 5pm Monday to Friday).

6.2.1. If the SAE is unexpected:

2. On receipt of a SAE form the clerical team (or delegate) forwards the SAE to the Trial Manager immediately. If they are absent, the CI should be informed directly.

3. The study manager, will inform the CI immediately (within 24 hours of receiving the SAE form).

4. If the PI has not already done so, the CI should review the SAE form and assess for relationship to the study. The CI will record their opinion and sign and date the SAE Report form.

5. After assessment if the SAE is found to be related to the study the CI/Trial Manager will report the SAE to the REC (Berkshire South Central REC) and study sponsor (Sheffield Teaching Hospitals) at using the SAE Report form for non-IMP studies (see Appendix 3) within 15 days of being notified of the SAE. If the SAE is not related to the study, the SAE is filed at the CTRU and no further reporting is required.

6.2.2. If the SAE is expected (listed in appendix 1) and the PI/Research Nurse/Midwife or another suitably trained member of the research team has confirmed this:

The SAE should be recorded in the eCRF. The SAE does not need to be reported to the CTRU.

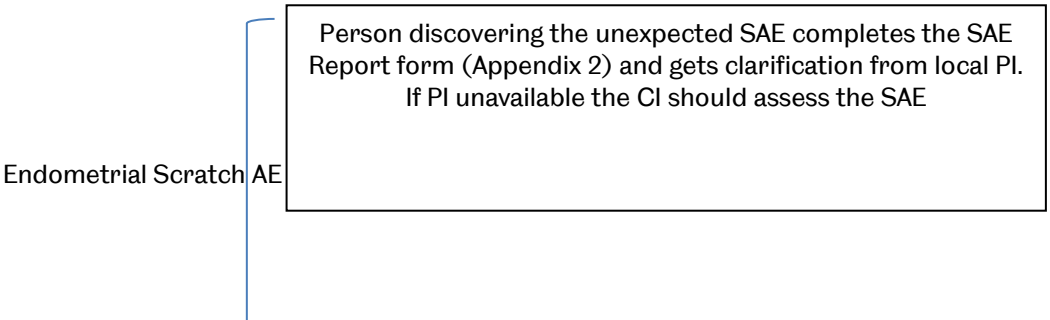
Note: The PI can delegate to the Research Nurse/Midwife or another member of the research team the responsibility for reporting Expected SAE's in the eCRF. This role should be delegated to a suitably trained and experienced member of the team and the delegation log should be completed accordingly to state this. In the absence of this it is the PI's responsibility.

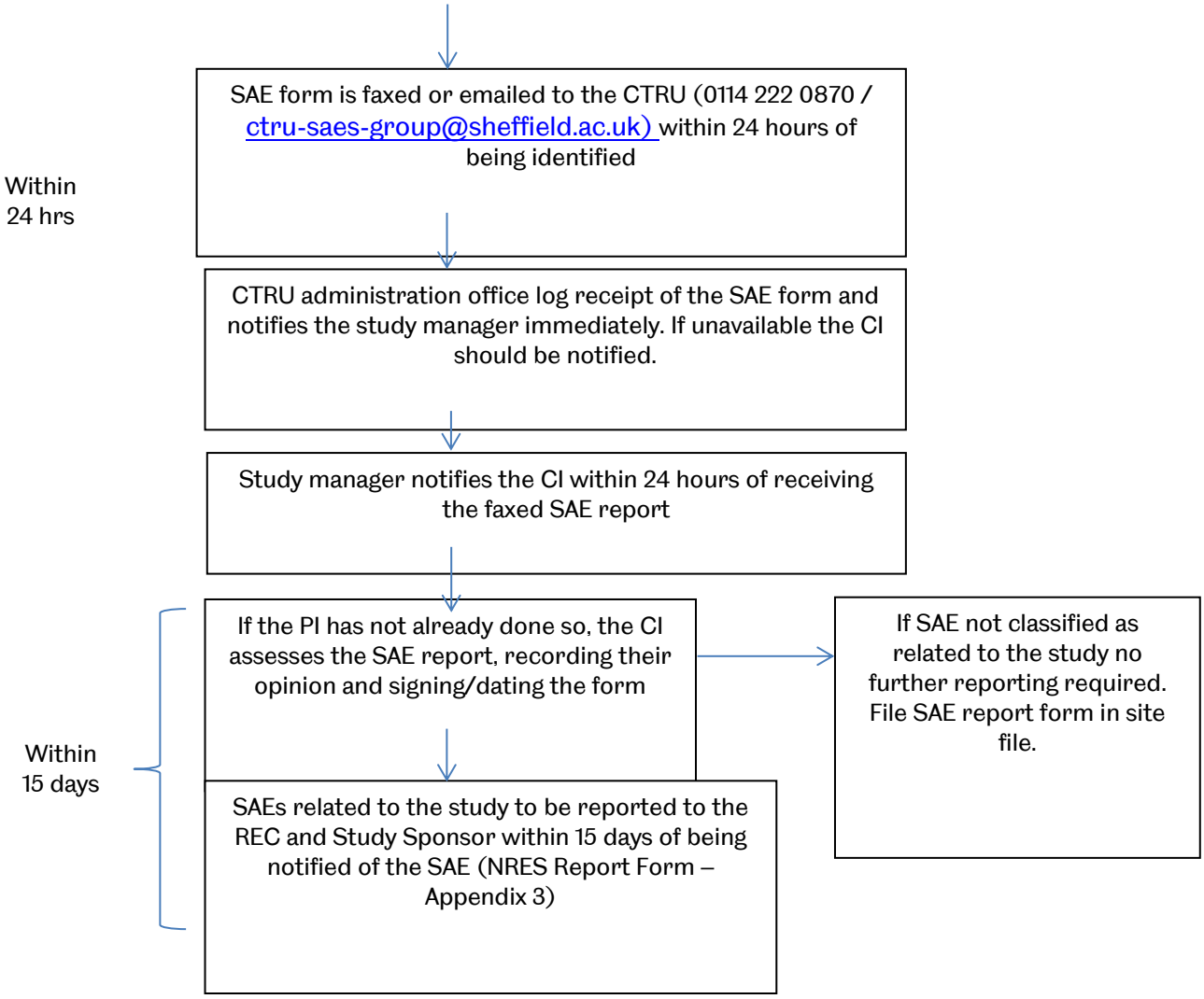
6.3 SAES related to the baby

SAEs regarding neonatal death (up to 6 weeks post-partum) and congenital abnormalities will be collected using the "Neonatal Serious Adverse Event Form" on the trial database as soon as possible after the 6 week post-partum follow-up.

Common minor congenital anomalies detected antenatally or postnatally (as defined by the EUROCAT minor anomaly exclusion list) will not be included as 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).

Figure .1. Flow Chart for unexpected SAE reporting procedure from a site





Appendix 1
Expected AEs

The following is a list of expected AE's related to pregnancy that will be documented on an ongoing basis in the eCRF. This is not finite list and upon discussion with the CI can be added to.

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

Expected SAEs

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

Appendix 2

Adverse event

ES ☐☐/☐☐☐

Adverse event details

Event

Any additional information

Start date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

End date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

OR ☐ ongoing (at end of study)

Serious? ☐ Yes* ☐ No

A serious adverse event is any untoward medical occurrence or effect that
- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity.

*Serious adverse event details

Seriousness	Frequency	Intensity	Outcome
☐ Death†	☐ Isolated	☐ Mild	☐ Recovered
☐ Life threatening	☐ Intermittent	☐ Moderate	☐ Improved
☐ Inpatient hospitalisation†	☐ Continuous	☐ Severe	☐ Unchanged
☐ Prolongs hospitalisation	☐ Unknown		☐ Deterioration
☐ Persistent or significant disability/incapacity			☐ Persisted
			☐ Death†

†Date of death ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

CI / PI assessment

Expected SAE? ☐ Yes ☐ No *(report to Sheffield CTRU)*

Relationship to endometrial scratch (intervention participants only)

☐ Definite	☐ Unlikely
☐ Probable	☐ Unrelated
☐ Possible	☐ Not assessable

Version 1 Formatted by The University of Sheffield CTRU <page number>

Adverse event

ES ☐☐/☐☐☐

‡ Hospital admission

Details

Start date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

End date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

OR ☐ ongoing (at end of study)

Report details

Date site staff became aware of the event ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Report type	Report date	Reason for update(s)	Reporting person		
			Signature	Name	Position
Initial report	__/__/____				
Follow up report	__/__/____				
Follow up report	__/__/____				

Concomitant medications

Record details of any concomitant medications which could help in the clinical judgement of this SAE

Medication name	Route	Dose	Unit	Freq	Start date	(✓ Ongoing or) End date
					__/__/____	☐ __/__/____
					__/__/____	☐ __/__/____
					__/__/____	☐ __/__/____

Signature

PI signature _____ PI name _____ ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Appendix 3

Health Research Authority

REPORT OF SERIOUS ADVERSE EVENT (SAE)
(For all studies except clinical trials of investigational medicinal products)

The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event.

1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
Email:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
Main REC reference number:	
Research sponsor:	
Sponsor's reference for this report: (if applicable)	

3. Type of event
Please categorise this event, ticking all appropriate options:

Death ☐	Life threatening ☐	Hospitalisation or prolongation of existing hospitalization ☐
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other ☐

4. Circumstances of event

Date of SAE:	
Location:	
Describe the circumstances of the event: *(Attach copy of detailed report if necessary)*	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

5. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	

6. Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report)
Copy to be kept for information by main REC.

Appendix 4

Neonatal serious adverse event

ES ☐☐/☐☐☐

Details

Baby number (from 'Pregnancy outcome' form) ☐

Event type(s)

☐ Severe congenital abnormality* → date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

☐ Neonatal death → date of death ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Details *(supporting information for event)*

** Abnormalities not listed on the EUROCAT minor anomaly exclusion list are considered 'severe'*

Signature

PI signature | PI name | d d m m y y y y