Endometrial Scratch – Protocol Non-compliance

1. Purpose

This guideline describes the procedure for recording, managing and reporting protocol non-compliances that occur in the Endometrial Scratch trial. This document summarises the procedures outlined in the Sheffield Clinical Trials Research Unit Standard Operating Procedure (SOP) for Protocol and GCP non-compliances (PM011 V2.0) and Serious Breach of Trial Protocol (PM007 V2.0) must therefore be used in conjunction with this SOP.

2. Background

A protocol non-compliance is any unplanned departure from the approved study protocol. Poor compliance can lead to patient safety being compromised, the data being rejected by the regulatory bodies and may affect the insurance or indemnity for the research project. Also if there is poor compliance this is an issue for the funder of the research and also may lead to difficulties with publication of the research.

3. Definitions

- A "*protocol non-compliance*" is a departure from the protocol or GCP that has been identified retrospectively
- A "*serious breach*" is a breach, of either the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, which is **likely** to effect to a significant degree –
  (a) the safety or physical or mental integrity of the subjects of the trial; or
  (b) the scientific value of the trial.

4. Reporting and assessment procedures for protocol violations

Who?

This SOP applies to any staff involved in the conduct of the Endometrial Scratch trial to whom non-compliances may become apparent including Principal Investigators, Research Nurses and Administrators.

4.1 Reporting at site

Any member of the study team may notice a non-compliance or serious breach. Upon doing so they should inform the local Principal Investigator. The Trial manager may also be informed at this stage, particularly if the local PI is temporarily unavailable or the site wants advice on dealing with the issue. The Principal Investigator and or the Trial Manager can then decide if it is a serious breach or a major, minor or file-note non-compliance.

a. The CTRU Trial Manager must be informed as soon as possible. To do this, a 'noncompliance form' (see appendix 1) should be completed and faxed/emailed to the CTRU, by the person who has identified the non-compliance. Any urgent measures taken at Site should be included on the form. The form should be signed and dated by the member of staff reporting the non-compliance. The Principal Investigator at Site should be informed by a member of Site staff, if not already aware.

b. Copies of all completed forms, and any updated versions (e.g. including assessments or where further actions have been taken) should be stored in the Site file.
c. A 'Site non-compliance log' (appendix 2) and 'Central non-compliance log' (appendix 3) should be kept in the site file.

4.2 Assessment at Sheffield CTRU:

Upon receipt of a non-compliance form, once logged, the CTRU Trial Manager should inform the Sponsor and Chief Investigator, where required (see section 5). Events should be assessed as a serious breach, major noncompliance, minor non-compliance, or downgraded to file note status. Where persistent, systematic or deliberate non-compliance(s) have occurred, affecting the safety of subjects or the scientific integrity of the trial, this may constitute a **serious breach**.

5. Examples of non-compliances and serious breaches in the Endometrial Scratch trial

The following is a list of the typical types of protocol non-compliances and serious breaches you may encounter during the trial. This list is not exhaustive. Please ask the study manager if you have any queries as to what may constitute a violation or deviation.

Examples:

Possible protocol non-compliances in the Endometrial Scratch trial:

- Endometrial Scratch intervention delivered at incorrect time of menstrual cycle.
- Failure to document informed consent correctly.
- Consent obtained, but witness of consent dated as prior to patient consent.
- Consent taken by person not appropriately trained in GCP or Endometrial Scratch trial procedures.
- Consent taken by person not listed on the trial delegation log.

Possible serious breaches in the Endometrial Scratch trial:

- Trial intervention (or any other study procedure including baseline data collection) commenced prior to consent into the study.
- Repetitions of the same protocol non-compliance.

6. Management at Sheffield CTRU

- Non-compliance forms will be sent to the sponsor and CI when the non-compliance is deemed to be a serious breach or major.
- All non-compliance forms will be filed in the Trial Master File (TMF).
- A central non-compliance log should be kept in the TMF and a site non-compliance log stored in the Site File. Both forms should be reviewed regularly, and repetitions of the same non-compliances identified.
- If the non-compliance is a serious breach, the sponsor and ethics committee should be notified within seven days of CTRU becoming aware of it. A CAPA (corrective and preventative action) plan should be put in place to deal with the serious breach (appendix 4). The CAPA owner would normally be the Trial Manager or Chief Investigator and approval of CAPA would normally come from the Chair of the Trial Steering Committee or the CTRU Director or Assistant Director. A copy of the documentation relating to the

serious breach should be kept in the trial master file and also circulated to study oversight committees. The central and site 'non-compliance logs' should also be updated.

- Where participant safety has been compromised, **urgent safety measures** may be required PM009 Urgent Safety Measures).

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Appendix 1

Non-compliance Form

Study details:

Study title (acronym):			
Sponsor:			
Site:			
REC reference:		R&D reference:	
Sponsor reference:		Chief Investigator (CI):	
Principal Investigator (PI):			

Non-compliance report:

Participant Study Number:		Participant initials:	
Date of event:		Date event identified:	
Date of report:		Date PI informed:	
Description:			
Immediate actions taken (if applicable):			
Reported by:			
Signature:		Date:	

CONTINUED OVERLEAF, TO BE COMPLETED BY CTRU...

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Assessment and further actions (to be completed by OTRU):

Assessment (please circle):	Serious breach / Major / Minor / File note		
Date of assessment:			
Explanation of assessment:			
Further actions taken and reasons for these (if applicable):			
Sponsor Informed: *(If required)*	Yes / No / N/A	Date:	
CI informed: *(if required)*	Yes / No / N/A	Date:	
Ethics Informed: *(If required)*	Yes / No / N/A	Date:	
Competent authority informed: (If required)	Yes / No / N/A	Date:	
Further information (e.g. CI or sponsors comments)			

Study Manager: _____ Date: _____

Sponsor (if required): _____ Date: _____

Chief Investigator (if required): _____ Date: _____

Date non-compliance form fed back to Site: _____

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Appendix 2

Site non-compliance log (to be stored in Site File)

Study title (acronym)		Sponsor:	
REC reference:		Chief investigator (CI):	
Site:		R&D reference:	
Principal investigator (PI):			

Part ID	Date of event	Date reported to CTRU	Date PI informed	Date completed non-compliance form fed back to Site	Assessment (to be formally assessed by CTRU and Site informed)		Actions taken*
					Assessment	Date assessed	

*Treatment stopped, =S; treatment dose altered (specify) = D; Withdrawn from study = W; Staff training undertaken = T; Protocol amendment = A; No action=N; and Other = O (please describe)

(This list is not exhaustive and should be tailored for each study)

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Appendix 3

Central non-compliance log (to be stored in TMF)

Study title (acronym):		Sponsor:	
Chief Investigator (CI):		REC reference:	

Subject ID	Site	Date of event	Date reported to CTRU	Category of non-compliance*	Assessment (Serious Breach, Major, Minor, File Note)		Date non-compliance form fed back to Site	Date informed (or state N/A if not required)				Actions taken**
					Assessment	Date assessed		Sponsor	CI	REC	Competent Authority	

*Eligibility = E, Missed windows = MW, consent = C, IMP issues = IMP, Other = O (please describe)

**Treatment stopped, =S; treatment dose altered (specify) = D; Withdrawn from study = W; Staff training undertaken = T; Protocol amendment = A; No action=N; and Other = O (please describe)

(These lists are for guidance and should be tailored for each study, as appropriate)

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Appendix 3

The University Of Sheffield. Clinical Trials Research Unit.

Corrective and Preventive Action (CAPA) Report

CAPA Owner (person responsible for overseeing CAPA):

Date of CAPA meeting(s):

Present at CAPA meeting(s):

Identification of Issue

Person identifying issue:
Trial issue relates to:
Date issue identified:
Description of issue:
Can the root cause of issue be identified?
Is further investigation required to understand root cause?
Root cause is:
Is it possible that this issue is still occurring in this trial? (e.g. at another site?)
Is this an issue which could be occurring in other CTRU trials?

Action Plan

Have any actions already been taken, if so what are they?
Corrective actions to be taken:
Actions required to prevent issue occurring again:
What it is the timetable for carrying out this action?

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What are the risks of carrying out this action?
How will success of this action be evaluated? (*If possible provide clear metrics which can be used objectively and state when evaluation should be carried out*).

Agreement to planned CAPA:

CAPA Owner: name & title	**date :**
Signature:	
Approved by: name & title	**date :**
Signature	

Date CAPA action implemented:
Report on effectiveness of CAPA:

Agreement that CAPA has been effective

CAPA Owner: name & title	**date :**
Signature:	
Approved by: name & title	**date :**
Signature	