1. PURPOSE

This document describes the procedure in NHS Fife for the management of breaches of Good Clinical Practice (GCP) or the approved clinical research protocol and complies with the principles of GCP for clinical research studies.

It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the Research & Development (R&D) pages on the NHS Fife Intranet (www.nhsfife.org/research) or for guidance, contact the R&D Department via fife-uhb.randd@nhs.net.
2. APPLICABILITY

Unless otherwise specified in a site agreement, this SOP applies to all members of staff associated with and managing any clinical research studies conducted in NHS Fife.

3. POLICY

3.1 Protocol and GCP breaches occurring in research studies can be serious or non-serious in nature. Not every deviation from the Protocol represents a serious breach that must be reported to the regulatory authorities – the majority are technical deviations that do not result in harm to the study subjects or significantly affect the scientific value of the reported results of the study. Breaches of this type, while they must be documented, are not serious breaches or reportable.

A serious breach is defined as a breach that is likely to significantly affect:
- the safety or physical or mental integrity of the subjects of the study.
- the scientific value of the study.

For example:
- Persistent non-compliance with GCP or the protocol that has a significant impact on the integrity of clinical research subjects in the UK or on the scientific value of the study.
- Failure to control or to account for Investigational Medicinal Products (IMPs) such that trial subjects are put at significant risk or the scientific value of the trial is compromised.
- Failure to report adverse events (AEs) or adverse reactions (ARs) in accordance with legislation, such that trial subjects, or the public, are put at significant risk.
- Proof of fraud relating to clinical research records or data.

3.2 For Clinical Trials of Investigational Medicinal Products (CTIMPs), the Medicines for Human Use (Clinical Trial) Regulations 2004 state that serious breaches of GCP or trial protocol must be reported by the Sponsor (or a person legally authorised by the Sponsor to perform this function) to the Medicines and Health Care Products Regulatory Agency (MHRA) within 7 days of the Sponsor becoming aware of the breach. In accordance with the HRA Standard Operating Procedures for Research Ethics Committees (https://www.hra.nhs.uk/about-us/committees-and-services/research-ethics-committee-standard-operating-procedures/) they must also be reported by the Sponsor to the Research Ethics Committee (REC) that originally granted approval within 7 days of the matter coming to their attention.


3.3 For non-CTIMPs research, the UK Policy Framework for Health and Social Care Research requires all research to be run to the principles of GCP and serious breaches of GCP or the protocol should be reported to the REC that originally granted approval in accordance with the HRA Standard Operating Procedures for Research Ethics Committees (https://www.hra.nhs.uk/about-us/committees-and-services/research-ethics-committee-standard-operating-procedures/).

3.4 All breaches of GCP or study protocol (serious and non-serious) must be documented in the Trial Master File (TMF) and/or Investigator Site File (ISF) by the Cl/PI.
3.5 For NHS Fife Sponsored studies the CI must also report any breaches to the funder if it is a condition of the agreement.

3.6 All serious breaches occurring on studies conducted in NHS Fife (sponsored and hosted) will be reported to the NHS Fife Research Governance Group for consideration. If deemed appropriate by the Research Governance Group, the NHS Fife R&D Department may carry out a full audit of the study and its management systems and procedures.

4. PROCEDURE

4.1 IDENTIFYING, RECORDING AND NOTIFYING A BREACH TO THE SPONSOR (NHS FIFE SPONSORED STUDIES)

4.1.1 The Sponsor, Chief Investigator (CI), Principal Investigator (PI) are responsible for providing overall supervision of the study and ensuring it is being conducted in accordance with the principles of GCP and the relevant regulations. They should also ensure that the study team are aware of the definition of a serious breach.

4.1.2 All deviations and breaches, both serious and non-serious, must be documented on a study specific Breach and Deviation Log (Doc Ref 22-01, Breach and Deviation Log) by the CI/PI or delegate.

4.1.3 If the breach is clearly or potentially serious, it must be reported to the Sponsor, via the Assistant R&D Director within 24 hours. If the Assistant R&D Director is unavailable another appropriate member of the R&D team (i.e. Lead R&D Research Nurse) will carry out the requirements detailed in this SOP.

4.1.4 Initial reporting can be carried out via telephone, email or in person. This can be done by telephoning the R&D Department on 01383623623 ext 20955 or the notification form can be emailed to fife-uhb.randd@nhs.net.

4.1.5 The Assistant R&D Director will request the person reporting the breach to complete a Potential Serious Breach Notification Form (Doc Ref 22-02) on the same day if possible or on the next day at least and email the completed form to the Assistant R&D Director.

4.1.6 Receipt of the initial Potential Serious Breach Notification Form will be acknowledged by the Assistant R&D Director by email.

4.1.7 The Assistant R&D Director will conduct an initial review and make the information available to any other necessary parties e.g. Clinical Trials Pharmacist.

4.1.8 The Assistant R&D Director must convene an NHS Fife R&D Review Group to work with the CI to assess the potential serious breach. The Review Group should:

- Normally include at least three people. Where possible this should include the Assistant R&D Director, R&D Research Coordinator and R&D Trials Facilitator
- Consult experts if required e.g. Data Manager, Statistician
- Identify which section of GCP or the protocol has been breached and how this may impact on the safety or physical or mental integrity of the study participants, or the scientific value of the study
- Reach a consensus as to whether the breach fulfils the criteria for a serious breach. The assessment will include review of any previous deviations/violations
to ascertain whether this is an isolated /systematic incident, patient (s) harmed or put at risk and impact on scientific integrity of the study.

- Discuss any required corrective and preventative actions (CAPAs) and initiate any Urgent Safety Measures (USMs) that may be required, and advise if a substantial amendment is required to temporarily halt the study.

4.1.9 If the CI disagrees with the Review Group’s decision regarding seriousness, an independent arbiter will be asked to provide an opinion. An independent arbiter can be the NHS Fife R&D Director or a senior researcher in another Board.

4.1.10 Where appropriate, the Assistant R&D Director on behalf of the Sponsor will contact the MHRA by telephone to discuss the serious breach.

4.1.11 Within two working days of receipt of the Potential Breach Notification Form, the Assistant R&D Director will update the Potential Breach Notification form to document the Review Group’s opinion as to whether the breach should be deemed serious, non serious or not a breach and outline the agreed Breach CAPA Plan. The updated form will then be circulated by email to the Review Group and the CI.

4.1.12 The completed Potential Serious Breach Notification Form must be filed in the Sponsor File and TMF.

4.2 REPORTING AND ESCALATION OF A SERIOUS BREACH (NHS FIFE SPONSORED STUDIES)

4.2.1 If the breach is confirmed as serious, the Assistant R&D Director, on behalf of the Sponsor, must notify the MHRA (CTIMPs only) and REC (both CTIMPs and non-CTIMPs) within 7 calendar days of the Assistant R&D Director becoming aware of the breach.

4.2.2 Any USM should be communicated to the MHRA (CTIMPs only) and REC (both CTIMPs and non-CTIMPs) immediately. The MHRA advise that Sponsors phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist. The Sponsor must then follow-up with notification in writing within three calendar days of the action being taken. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

4.2.3 Serious Breach Reporting for CTIMPs

4.2.3.1 A Notification of Serious Breach of Good Clinical Practice or Trial Protocol form (available from https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach) should be completed and submitted by email to the MHRA (GCP_SeriousBreaches@mhra.gsi.gov.uk) and REC.

4.2.3.2 Consideration should also be given to whether there are any other relevant MHRA units that should be notified to comply with other legislation (for example, notification to the MHRA Clinical Trials Unit (CTU) if the breach constitutes a USM or if a substantial amendment is required due to a temporary halt in the study or to the Defective Medicines Report Centre if the breach involves defective medicines or IMP recall etc.)

4.2.3.3 Once the initial notification has been submitted, the Sponsor will continue to review the serious breach to identify any additional pertinent information and will update the breach notification to the MHRA and REC as appropriate.
4.2.3.4 If the MHRA requests any additional information such as a copy of the protocol, REC Application and/or SOPs, the Assistant R&D Director on behalf of the Sponsor will liaise with the CI and the study team to obtain the additional documents and will submit them to the MHRA.

4.2.4 Serious Breach Reporting for Non-CTIMP Studies

4.2.4.1 A Notification of Serious Breach of Good Clinical Practice or Study Protocol to Research Ethics Committee (REC) Form (Doc Ref 22-03) should be completed and submitted by email to the REC that gave the original approval for the study.

4.2.4.2 Consideration should also be given to whether the breach constitutes a USM or if a substantial amendment is required due to a temporary halt in the study.

4.2.4.3 Once the initial notification has been submitted, the Sponsor will continue to review the serious breach to identify any additional pertinent information and will update the breach notification to the REC as appropriate.

4.2.4.4 If the REC requests any additional information the Assistant R&D Director on behalf of the Sponsor will liaise with the CI and the study team to obtain the additional documents and will submit them to the REC.

4.3 FOLLOW-UP OF SERIOUS BREACHES (NHS FIFE SPONSORED STUDIES)

4.3.1 Appropriate corrective and preventative actions will be implemented and any further information on the breach notified to the MHRA and/or REC. Any follow up reports should be

• Clearly identified as a follow up
• Identify the unique reference number given by the MHRA and/or REC on acknowledgement of initial report
• Be sent directly to the person dealing with the initial query (unless otherwise instructed).

4.3.2 The Assistant R&D Director will prepare a report for consideration by the Research Governance Group (RGG) providing a summary of the breach and the progress of the Breach CAPA plan.

4.3.3 If the Breach CAPA Plan is not progressing according to agreed timelines, the Assistant R&D Director will escalate the lack of progress to the R&D Director.

4.3.4 When all corrective actions required have been addressed, the Assistant R&D Director will close the Breach CAPA Plan and sign the Proposed Serious Breach Notification Form to confirm this. The closed Breach CAPA Plan will be filed in the Sponsor File and SMF.

4.3.5 If the study has been temporarily halted, the CI will be advised of when the study may re-commence. Recomencement may be subject to additional monitoring of the study by the Sponsor.

4.3.6 Copies of all correspondence relating to the breach will be securely retained by the R&D Department in the relevant study Sponsor File.
4.4 RECORDING AND REPORTING A BREACH FOR HOSTED STUDIES

4.4.1 If a suspected serious breach is identified by the research team or via audit, it should be reported to the study Sponsor contact by the PI, delegate or other **within 24 hours** of the breach being identified.

4.4.2 Initial reporting can be carried out via telephone, email or in person.

4.4.3 Where available the PI should follow the Protocol or the Sponsor’s own instructions to report the serious breach. Otherwise all breaches should be documented using the NHS Fife Potential Serious Breach Notification Form (Doc Ref 22-03). A copy of the completed form should be filed within the ISF.

4.4.4 The R&D Department must also be notified by the research team that a suspected serious breach has occurred within NHS Fife. This can be done by telephoning the R&D Department on 01383623623 ext 20955 or the notification form can be emailed to fife-uhb.randd@nhs.net.

4.4.5 A member of the R&D Department will acknowledge receipt of the notification. It is the responsibility of the reporting individual to contact the R&D Department if no acknowledgement is received.

4.4.6 The CI/PI will be responsible for ensuring that the R&D Department is notified of the Sponsor assessment of the reported suspected serious breach and details of any CAPA plan as soon as this is confirmed.

4.4.7 In situations where there may be disagreement between the investigator and external Sponsor over the assessment of a serious breach, NHS Fife will exercise due diligence and give consideration as to whether it has a responsibility to direct report to the Regulatory Authorities. This decision will be made by the Assistant R&D Director (or delegate) and documented in the Investigator Site File.

4.4.8 All non-serious breaches should be documented as described in section 4.1.2 unless Sponsor specific instructions exist.

5. REVIEW OF ALL SERIOUS BREACHES

The R&D Research Coordinator (or alternate) will undertake a review every 6 months of all suspected serious breaches which have been reported to the R&D Department (including both sponsored and hosted studies). This review will aim to identify any pattern of related breaches that need to be addressed by the R&D the Sponsor or reported to the Regulatory Authorities and will be documented in the ‘Suspected Breaches Folder’ and circulated to the Research Governance Group. Copies of any resulting notifications should also be filed in the Suspected Breaches Folder’.

6. ASSOCIATED DOCUMENTS

Doc Ref 22-01 - Breach and Deviation Log
Doc Ref 22-02 - Potential Serious Breach Notification Form
Doc Ref 22-03 - Notification of Serious Breach of Good Clinical Practice or Study Protocol to Research Ethics Committee (REC) Form
7. ABBREVIATIONS

AE    Adverse Event
AR    Adverse Reaction
CAPA  Corrective and Preventative Actions
CI    Chief Investigator
CTIMP Clinical Trial of Investigational Medicinal Product
ISF   Investigator Site File
MHRA  Medicines and Health Care Products Regulatory Agency
PI    Principal Investigator
REC   Research Ethics Committee
R&D   Research & Development
SOP   Standard Operating Procedure
TASC  Tayside Medical Science Centre
TMF   Trial Master File
USM   Urgent Safety Measure

8. REFERENCES

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects. (http://www.wma.net/en/30publications/10policies/b3/)

It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.


Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol (http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf)

Appendix 1

Flowchart for Managing Breaches

Member of study team, monitor, auditor etc becomes aware of breach

Record in Breach and Deviation Log (Doc Ref 22-01)

Not serious

Serious or potentially serious

Complete Potential Serious Breach Notification Form (Doc Ref 22-02) and report to Assistant R&D Director who will assess

Not serious

Serious or potentially serious

Document in Sponsor/R&D file and in TMF/ISF

Fife Sponsor

Set up R&D Review Group to assess and discuss CAPAs and USMs with 2 days

Inform REC and MHRA (if CTIMP)

Implement CAPAs

External Sponsor

Inform Sponsor