STANDARD OPERATING PROCEDURE FOR MANAGEMENT OF BREACHES OF GCP OR THE STUDY PROTOCOL FOR CLINICAL RESEARCH

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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

This SOP applies to all members of staff associated with and managing **any** clinical research study 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.
- 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/res-and-recs/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.

Further information is available from the MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdf).

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/res-and-recs/research-ethics-committee-standard-operating-procedures/).

3.4 All breaches of GCP or study protocol (serious and non-serious) must be documented in the Study Master File (SMF) and/or Investigator Site File (ISF) by the Chief Investigator (CI) or delegate for studies sponsored by NHS Fife or the Principal Investigator (PI) or delegate for studies hosted by NHS Fife.

3.5 For NHS Fife Sponsored studies the CI must also report any breaches to the funder if it is a condition of the funding agreement.

3.6 All breaches categorised as **Serious** occurring on studies conducted in NHS Fife (sponsored and hosted) must be reported by the CI/PI or delegate to the NHS Fife R&D Department for consideration. If deemed appropriate by the Assistant R&D Director, the NHS Fife R&D Department will 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 and CI/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 is aware of the definition of a Serious Breach.

4.1.2 All breaches, both serious and non-serious, must be documented on a study specific Breach Log (Doc Ref 22-01) 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 NHS Fife R&D Department within 24 hours by the CI/PI or delegate.

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 01383 623623 ext 20955 or by emailing fife.randd@nhs.scot.

4.1.5 The person reporting the breach must complete a Potential Serious Breach Notification Form - Sponsored Studies (Doc Ref 22-02) on the same day if possible or on the next day at least and email the completed form to the R&D Department (fife.randd@nhs.scot).

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

4.1.7 The R&D Quality & Performance Lead must immediately inform the Assistant R&D Director and make the information available to any other necessary parties.

4.1.8 The R&D Quality & Performance Lead 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, Lead R&D Research Nurse and R&D Quality & Performance Lead.

- Consult experts if required e.g. Data Manager, Statistician.

- Review the breach and identify which principle of GCP or section of the protocol has been breached and how this may impact on (i) the safety or physical or mental integrity of the study participants, or (ii) the scientific value of the study. A variety of factors will be considered e.g. the design of the study, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc.

The assessment will include a review of any previous breaches to ascertain whether this is likely to be an isolated or systematic incident.

- Reach a consensus as to whether the breach fulfils the criteria for a serious breach.

- Discuss any required corrective and preventative actions (CAPAs), 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 Within two working days of receipt of the Potential Breach Notification Form, the R&D Quality & Performance Lead will complete a Breach Assessment Form – Sponsored Studies (Doc ref 22-04) 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. This form will then be circulated by email to the Review Group and the CI.

4.1.11 The Potential Breach Notification Form and Breach Assessment Form must be filed in the Sponsor File and SMF by the CI or delegate.

4.1.12 Copies of the completed Potential Serious Breach Notification Form, Breach Assessment Form and any associated correspondence must be filed by the R&D Quality & Performance Lead in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES.

4.1.13 Details of the Breach and agreed CAPA plan must be added to the CAPA log held in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES by the R&D Quality & Performance Lead and all actions followed up until closure.

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 REC **within 7 calendar days** of the Assistant R&D Director becoming aware of the breach.

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

4.2.3 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 Any USM should be communicated to the REC immediately by the Assistant R&D Director on behalf of the Sponsor.

4.2.5 If the Review Group determines that the reported event may constitute research fraud or misconduct the NHS Fife Policy GPR3 must be followed.

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

4.3.1 Once the initial notification has been submitted, the Assistant R&D Director must continue to review the serious breach to identify any additional pertinent information and update the breach notification to the REC as appropriate.

4.3.2 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.

4.3.3 Appropriate corrective and preventative actions must be implemented and any further information on the breach notified to the REC. Any follow up reports should be:

- Clearly identified as a follow-up.
- Identify the unique reference number given by the REC on acknowledgement of initial report.

- Be sent directly to the person dealing with the initial query (unless otherwise instructed).

4.3.4 If the Breach CAPA Plan is not progressing according to agreed timelines, the R&D Quality & Performance Lead must escalate the lack of progress to the Assistant R&D Director.

4.3.5 When all corrective actions required have been addressed, the R&D Quality & Performance Lead must update the CAPA log and email a copy of the final Breach Report and Breach Assessment Form to the CI and Assistant R&D Director to confirm that the Breach has been closed. A copy of this email must be filed in the Sponsor File and SMF by the CI.

4.3.6 If the study has been temporarily halted, the CI will be advised by the Assistant R&D Director or delegate of when the study may re-commence. Recommencement may be subject to additional monitoring of the study by the Sponsor.

4.3.7 Copies of all correspondence relating to the breach will be retained by the R&D Quality & Performance Lead in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES.

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 monitoring or 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 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 and reported to the Sponsor using the NHS Fife Potential Serious Breach Notification Form – Hosted Studies (Doc Ref 22-05). A copy of the completed form and all associated correspondence must be filed by the PI or delegate within the ISF.

4.4.3 The R&D Department must also be notified by the PI or delegate that a suspected serious breach has occurred within NHS Fife. This can be done initially by telephoning the R&D Department on 01383 623623 ext 20955 or by emailing fife.randd@nhs.scot.

4.4.4 The person reporting the breach must also email a copy of the completed Breach Notification Form (Sponsor specific form or Doc Ref 22-05) to the R&D Department (fife.randd@nhs.scot) on the same day if possible or on the next day at least.

4.4.5 The R&D Department will acknowledge receipt of the notification within 2 working days. It is the responsibility of the reporting individual to contact the R&D Department if no acknowledgement is received.

4.4.6 The R&D Quality & Performance Lead must immediately inform the Assistant R&D Director and Lead R&D Research Nurse (if the study involves R&D Research Nurses) and make the information available to any other necessary parties.

4.4.7 The PI or delegate must notify the R&D Department (fife.randd@nhs.scot) of the Sponsor Assessment and provide details of any CAPA plan as soon as this is confirmed.

4.4.8 The R&D Quality & Performance Lead, Assistant R&D Director and Lead R&D Research Nurse (if the study involves R&D Research Nurses) will conduct an initial review of the potential serious breach to ascertain whether this is an isolated/systematic incident and the extent to which any participant(s) was harmed or put at risk. In collaboration with the PI they will also assess the need to initiate any Urgent Safety Measures (USMs) that may be required.

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

4.4.10 The R&D Quality & Performance Lead will complete a Breach Assessment Form – Hosted Studies (Doc Ref 22-06) to document the outcome of the review by the R&D Department and outline the agreed Breach CAPA Plan. This form must then be circulated by email to the PI.

4.4.11 Details of the Breach and agreed CAPA plan must be added to the CAPA log held in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES by the R&D Quality & Performance Lead and all actions followed up until closure.

4.4.12 Copies of all notifications and related correspondence must be filed by the R&D Quality & Performance Lead in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES.

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

4.5 FOLLOW-UP OF SERIOUS BREACHES (NHS FIFE HOSTED STUDIES)

4.5.1 If the Breach CAPA Plan is not progressing according to agreed timelines, the R&D Quality & Performance Lead must escalate the lack of progress to the Assistant R&D Director.

4.5.2 When all corrective actions and preventative actions required have been addressed, the R&D Quality & Performance Lead must update the CAPA log and email a copy of the final breach report and breach assessment form to the PI and Assistant R&D Director to confirm that the Breach has been closed. A copy of this email must be filed in the ISF by the PI or delegate.

4.5.3 If the study has been temporarily halted, the PI will be advised by the Assistant R&D Director or delegate of when the study may re-commence. Recommencement may be subject to additional monitoring of the study by the Sponsor.

4.5.4 Copies of all correspondence relating to the breach will be retained by the R&D Quality & performance Lead in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES.

5. RECORDING ON DATIX

All breaches of study protocol and GCP which are deemed to have significantly affected the safety of patients or staff must be reported via DATIX by the CI (for studies sponsored by NHS Fife) or PI for studies hosted by NHS Fife).

6. ONGOING REVIEW OF ALL SERIOUS BREACHES

6.1 The R&D Quality & Performance Lead (or delegate) 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 Department. A report detailing the outcome of the review will be prepared by the R&D Quality & Performance Lead (or delegate) and circulated to the Assistant R&D Director and R&D Director.

6.2 A copy of the 6 monthly report must be filed by the R&D Quality & Performance Lead in S:\Research\QUALITY ASSURANCE\PROTOCOL & GCP BREACHES.

7. ASSOCIATED DOCUMENTS

Doc Ref 22-01 - Breach Log.
Doc Ref 22-02 - Potential Serious Breach Notification Form – Sponsored Studies.
Doc Ref 22-03 - Notification of Serious Breach of Good Clinical Practice or Study Protocol to Research Ethics Committee (REC) Form.
Doc Ref 22-04 - Potential Serious Breach Assessment Form – Sponsored Studies.
Doc Ref 22-05 - Potential Serious Breach Notification Form – Hosted Studies.
Doc Ref 22-06 - Potential Serious Breach Assessment Form – Hosted Studies.

8. 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
SMF	Study Master File
USM	Urgent Safety Measure

9. REFERENCES

Medicines for Human Use (Clinical Trials) Regulations 2004.
(*http://www.opsi.gov.uk/si/si2004/20041031.htm*).
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

Standard Operating Procedures for Research Ethics Committees
http://www.hra.nhs.uk/documents/2013/08/standard-operating-procedures-for-research-ethics-committees-sops.pdf

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*)

UK Policy Framework for Health and Social Care Research
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/.

10. DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of editions made:
1	Julie Aitken R&D Trials Facilitator	02 Feb 2015	New *(Adapted from TASC SOP 24, version 1 and TASC SOP 25, Version 7)*
2	Julie Aitken R&D Trials Facilitator	08 Jab 2018	Rewritten for clarity and to reflect current practice.
3	Julie Aitken R&D Quality & Performance Lead	14 Sept 2020	Amended for consistency with R&D SOP template. Procedure updated to reflect current practice. Contact details for R&D Department updated throughout. New associated documents Doc Ref 22-04, 22-05 and 22-06 added. Text refreshed throughout for clarity.

11. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research, Development & Innovation Director, NHS Fife Signature: 	07 Sep 2020