Standard Operating Procedure: Management of Deviations, Breaches and Urgent Safety Measures

SOP Number: UoA-NHSG-SOP-045
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Document History:

<table>
<thead>
<tr>
<th>Version No.</th>
<th>Description of Changes</th>
<th>Date Approved</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>New SOP (replacing UoA-NHSG-SOP-015 ‘Handling breaches of the trial protocol and/or GCP in interventional research projects’).</td>
<td>1-4-15</td>
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This SOP will be reviewed at least every 3 years from initial and subsequent issue dates.

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1. **PURPOSE/INTRODUCTION**

1.1 The purpose of this Standard Operating Procedure (SOP) is to describe the procedure for identifying and managing Deviations, Breaches (Serious and Non-Serious) and Urgent Safety Measures, identified as a non-conformance with an approved research protocol, and/or the principles of Good Clinical Practice (GCP).

1.2 This SOP complies with the Scottish Executive Health Department’s Research Governance framework for Health and Community Care (current version) and the requirements of the Medicine for Human Use (Clinical Trials) Regulations 2004 and 2006 (the UK Clinical Trial Regulations).

2. **SCOPE**

2.1 This SOP applies to all researchers and Sponsor staff participating in all studies sponsored or co-sponsored by University of Aberdeen (UoA) or NHS Grampian (NHSG). Interventional research projects include Clinical Trials of Investigational Medicinal Projects (CTIMP) falling under the Medicines for Human use (Clinical Trials) Regulations 2004 and related amendments, and other interventional studies (e.g. surgical studies, device studies, non CTIMP drug studies and any other projects deemed to be ‘interventional’ by the Sponsor).

2.2 UoA-NHSG SOPs may also be used by staff from other NHS areas, or organisations, with prior agreement.

2.3 For research projects which are sponsored externally to the UoA or NHSG, local researchers and support staff should refer to the respective Sponsor’s procedure and any timelines for handling Breaches and Urgent Safety Measures.

3. **RELATED DOCUMENTATION**

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<th>SOP Number</th>
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<tr>
<td>UoA-NHSG-SOP-003</td>
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<td>UoA-NHSG-SOP-020</td>
<td>Study Closure Including Procedure for the Sudden Closure or Suspension</td>
</tr>
<tr>
<td>UoA-NHSG-TMP-067</td>
<td>Breach Report form</td>
</tr>
</tbody>
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4. **REFERENCES**

- Scottish Executive Health Department Research Governance Framework for Health and Community Care 2006.
- UK Medicines for Human Use (Clinical Trials) Regulations 2004.
- National Research Ethics Service/Health Research Authority website.

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- Medicine and Healthcare Products Regulatory Agency website (MHRA). Current versions of these documents can be accessed via the Research Governance Website: http://www.abdn.ac.uk/medical/researchgovernance/clincialresearch

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

4.1 ABBREVIATIONS AND DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>CAPA</td>
<td>Corrective and Preventive Action</td>
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<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CSOG</td>
<td>Clinical Studies Oversight Group</td>
</tr>
<tr>
<td>CTIMP</td>
<td>Clinical Trials of Investigational Medicinal Product</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice (ICH)</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency</td>
</tr>
<tr>
<td>NHSG</td>
<td>NHS Grampian</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial/Project Master File</td>
</tr>
<tr>
<td>UoA</td>
<td>University of Aberdeen</td>
</tr>
</tbody>
</table>

5. DEFINITION OF A DEVIATION, BREACH (SERIOUS AND NON-SERIOUS) AND URGENT SAFETY MEASURES

5.1 It is the CI’s responsibility to ensure that all researchers adhere to the approved protocol, Sponsor SOPs and GCP at all times. The only exception is when a deviation is required for the safety of a participant (see Management and Reporting of Urgent Safety Measures at 12).

5.2 A **Breach** is a departure from the approved protocol, research project documentation, SOPs or any other information relating to the conduct of the trial. A **Non-Serious Breach** may be considered a ‘minor non-conformance’ or ‘violation’ and has no impact on a participants’ safety or wellbeing, and/or the scientific integrity of the research. No substantial amendment is required to the approved protocol, trial documentation or trial SOPs.

Examples of A Non-Serious Breach include:

- A study visit out with a defined schedule;
- Boxes on the consent form ticked rather than initialled;

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Misplaced consent form (completed but mis-filed).

A Non-Serious Breach may be upgraded, upon review, to a Serious Breach.

It should be noted that repeated Non-Serious Breaches which become systematic, or impact multiple participants, may be regarded as a Serious Breach and should be reported as such.

5.3 A **Serious Breach** is defined as a Breach which is likely to affect, or have the potential to affect, to a significant degree:
- The safety, physical or mental integrity of the research participants; and/or
- The scientific value of the research.

This definition is adapted from the Medicines for Human Use (Clinical Trial) Regulations 2004.

5.4 A **Deviation** is a minor deviation from an SOP or a planned event. Examples include:
- An SOP being used beyond its review date;
- An audit or monitoring visit taking place outside of schedule.

A Deviation may be upgraded, upon review, to a Non-Serious Breach or Breach.

5.5 An **Urgent Safety Measure** occurs when a research participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant(s). An Urgent Safety Measure does not have prior approval from REC, MHRA or the Sponsor.

5.6 Urgent Safety Measures must be reported to REC, MHRA and Sponsor immediately after they are implemented.

5.7 Deviations, Breaches and Urgent Safety Measures shall be recorded in such a way that their impact on the research project can be independently assessed during the conduct, reconstruction and reporting of the trial. Full details shall include any Corrective and Preventive Actions (CAPA) identified.

5.8 Relationship between a Deviation, Non-Serious Breach and Serious Breach.

A Deviation shall be reviewed by the Research Governance Team and/or QA and may be upgraded to a Non-Serious Breach.

A Non-Serious Breach shall be reviewed by Research Governance Team and/or QA and may be upgraded to a Serious Breach, or downgraded to a Deviation.

A Serious Breach shall be reviewed by Research Governance Team and/or QA and may be downgraded to a Non-Serious Breach, or a Deviation.

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6 PROCEDURE

6.1 A Deviation or Breach may be identified and reported by Sponsor or by CI/research team (to Sponsor). The CI, as Sponsor delegate, must ensure that potentially Serious Breaches of the research protocol and/or the principles of GCP are reported to the Sponsor within 24 hours of being identified. In a multi-site project, if such a breach has occurred at a remote investigational site, the PI shall report the Breach to the CI, and the CI to Sponsor within 24 hours.

6.2 The Sponsor is responsible for reporting Serious Breaches in CTIMPs and device studies to the MHRA within 7 calendar days of the Breach being notified to Sponsor.

6.3 For all research projects, the CI is responsible for reporting Serious Breaches to the relevant Research Ethics Committee (REC) within 7 calendar days of the Breach being confirmed as serious.

6.4 Deviations and Breaches shall be recorded on the Log of Deviations, Breaches and Urgent Safety Measures (Appendix 1) and Breaches reported using the Breach Report form (UoA-NHSG-TMP-067), unless previously agreed with Sponsor. The report shall include:

- An overview of the incident and its cause;
- Detail of Corrective and Preventive Action (CAPA);
- An assessment of the likelihood of a recurrence;
- An impact assessment on any work performed prior to the event, which may be compromised;
- Outline of any changes which may be required to the protocol;
- Likely timeline for CAPA and amendment approval (if applicable).

6.5 The CI shall make an initial assessment as to whether a Breach is Non-Serious or a Serious Breach (as defined above). The CI shall contact the Research Governance Manager who shall review and make a final assessment on seriousness, in liaison with the Quality Assurance Manager. If deemed a Serious Breach the Research Governance Manager shall set up a Breach Assessment Team to discuss the Breach and report to MHRA within 7 calendar days of the Breach being notified to Sponsor.

6.6 For all breaches, the completed Breach Report Form and updated Breach Report Log should be forwarded to the Research Governance Team within 24 hours of the CI becoming aware of the Breach to pharmaco@abdn.ac.uk. The Research Governance Team shall acknowledge receipt within 24 hours.

6.7 The CI of the research project is responsible for ensuring mechanisms are in place to monitor research activity and identify any deviations from the study protocol or GCP. The CI may share this responsibility with other members of the research team, or a steering committee. Any such arrangements which are in place should be
documented in the Investigator Trial Master File.

6.8 A log of Deviations, Breaches and Urgent Safety Measures (Appendix 1) must be available in the TMF and completed as necessary by the CI. The CI may delegate responsibility for completing the log to named persons on the study delegation log.

6.9 A Non-Serious Breach (i.e. not judged to impact participant safety and/or scientific integrity of the research project) should be noted in the TMF and/or Case Report Form (CRF) and source documents, explaining any actions taken and their justification.

6.10 Actions taken to investigate a Breach may include an audit of the affected area, an impact assessment to establish work which is/has been affected, and identifying CAPA and an appropriate CAPA plan. If the Sponsor identifies a Breach during routine audit/monitoring, they shall agree CAPA and may request an impact assessment to establish work which is/has been compromised.

6.11 If a Breach is deemed Serious the Sponsor may suspend the project until all necessary CAPA have been implemented.

7 SPONSOR ASSESSMENT AND FURTHER INVESTIGATION OF A BREACH

7.1 Where required, the Research Governance Manager, in liaison with the Quality Assurance Manager, will facilitate a systematic evaluation of the issue with a Breach Assessment Team comprising; the CI or PI, the lead physicians for the Sponsor(s), and key members of the research team (e.g. Trial Manager), as appropriate. The Breach Assessment Team will involve experts from within the Sponsor organisations or external parties as required. In some cases the Breach Assessment Team may request further investigation is carried out before an assessment can be made.

The assessment made by the Breach Assessment Team will:
- Confirm whether the Breach comprises a Serious Breach or not,
- Identify which section of GCP or the approved protocol has been breached,
- Identify how the Breach impacts on trial participants and/or the scientific integrity of the research.

7.2 The Breach Assessment Team will make a judgement whether to implement any Urgent Safety Measures, such as stopping the research project or specific aspects of the project immediately, pending any further investigation as necessary (see UoA-NHSG-SOP-020 ‘Study Closure Including Procedure for the Sudden Closure or Suspension of a Trial’). The CI retains the right to implement any urgent safety requirements before the Breach Assessment Team conducts its assessment.

7.3 The Breach Assessment Team will work with the CI to identify the extent of the Breach and make a CAPA plan. The Breach Assessment Team will agree who needs to be notified of the Breach and any follow up actions required. In addition, all records of assessments of potential Serious Breaches will be retained, even if these

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breaches were not deemed serious by the assessment team.

8 NOTIFICATION OF SERIOUS BREACH TO THE RELAVANT PARTIES

8.1 For all Interventional Studies the CI will inform the Project Management Group and, where applicable, the relevant Trial Steering Committee(s) and/or Data Monitoring Committee(s) of the Serious Breach. In certain situations only limited details of the Breach may be reported to the committees in order to maintain trial blinding.

8.2 The Research governance Manager (RGM) shall report all Interventional Study Breaches to the Clinical Studies Oversight Group (CSOG) at its next meeting or an extraordinary meeting called for this purpose.

8.3 The RGM will notify the MHRA of a serious breach using the Notification of Serious Breach template provided within the MHRA Serious Breach guidance (current version available on the MHRA website) http://www.gov.uk/good-clinical-practice-for-clinical-trials#report-a-serious-breach

Copies of all Serious Breach Notifications will be filed in the relevant Trial Master File (TMF) and the Sponsor files.

8.4 For all other Interventional Studies the CI will forward the Breach Report form (UoA-NHSG-TMP-66) and the Notification of Serious Breach template (MHRA) to the REC that provided the favourable opinion for the study, and the local NHS R&D departments for the sites where the Serious Breach occurred, copying in pharmaco@abdn.ac.uk.

9 CTIMPS: PROVIDING FOLLOW UP REPORTS TO THE RELEVANT PARTIES

9.1 The Research Governance Manager is responsible for follow up notifications to relevant authorities.

9.2 The Sponsor will keep the Breach under review in order to close out the agreed CAPA and identify any additional information and forward follow up reports to the MHRA, REC and local NHS R&D office(s), until the Breach is formally closed by MHRA.

9.3 The MHRA may request additional information (e.g. current protocol, standard operating procedures, corrective action plan). The CI/PI or delegated individual should provide all requested documents to the RGM, to be forwarded on to MHRA on behalf of the Sponsor.

10 PLANNING AND IMPLEMENTING CORRECTIVE AND PREVENTIVE ACTION

10.1 The Breach Assessment Team will liaise with the CI/PI to implement a CAPA plan to address the Breach.

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10.2 Dependent on the initial assessment of the extent and impact of the Serious Breach, the Breach Assessment Team may request that an audit is undertaken of the research project and/or associated programme of work and or additional research projects which may be impacted, including an assessment of management systems and procedures.

11 NON-SERIOUS BREACH

11.1 Non-Serious Breaches shall be referred by the Research Governance Manager to the Clinical Trials Facilitation Group (CTFG) for assessment and confirmation. The Research Governance Manager shall notify the CI of this outcome. The CTFG may, upon review, upgrade a Non-Serious Breach to a Serious Breach.

12 MANAGEMENT AND REPORTING OF URGENT SAFETY MEASURES

12.1 Under the Medicines for Human Use (Clinical Trials) Regulations 2004 the Sponsor, CI or PI may implement Urgent Safety Measures (USM) to protect trial participants from immediate harm. Where possible the CI or PI should decide on the appropriate action after discussion with a Co-Investigator and document this in the Investigator TMF or Site File.

12.2 Any Urgent Safety Measure (USM) relating to an Investigational Medicinal Product project must be notified to REC and MHRA within three days of the action being taken. The Sponsor and the QA Manager should be notified immediately, and before the MHRA and REC, to advise on the procedure and ensure they are aware of the details (should the REC or MHRA contact them directly for further information). The notification should describe the event, the measures taken and justification for the measures taken. The MHRA can be contacted via email at clinicaltrialshelpline@mhra.gsi.gov.uk and stating ‘Urgent Safety Measures’ in the subject title. The REC should be notified in writing and the Sponsor and QA Manager copied into communications. All communications should be copied to the TMF.
## Appendix - 1 Log of Deviations, Breaches and Urgent Safety Measures

<table>
<thead>
<tr>
<th>STUDY TITLE:</th>
<th>EUDRACT NUMBER:</th>
<th>CI:</th>
</tr>
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<tbody>
<tr>
<td>SITE NAME AND ADDRESS:</td>
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### Log of Deviations, Breaches and Urgent Safety Measures

<table>
<thead>
<tr>
<th>DATE INCIDENT ADDED TO LOG</th>
<th>INCIDENT DATE</th>
<th>PARTICIPANT NUMBER</th>
<th>DEVIATION, NON-SERIOUS BREACH, SERIOUS BREACH OR URGENT SAFETY MEASURE (USM)</th>
<th>SITE CORRECTIVE ACTION</th>
<th>SITE PREVENTIVE ACTION</th>
<th>DATE REPORTED TO SPONSOR</th>
<th>URGENT SAFETY MEASURE REPORTED TO MHRA, REC, R&amp;D QA</th>
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