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STU-SOP-TM-011 – Standard Operating Procedure on Identifying, Assessing and Reporting Deviations, Breaches and Urgent Safety Measures

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1 Abbreviations

BAT	Breach Assessment Team
CAPA	Corrective and Preventive Action
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring and Ethics Committee
DRG	Document Review Group
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principle Investigator
REC	Research Ethics Committee
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
SU	Swansea University
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
USM	Urgent Safety Measure

Deviation/Non-Serious Breach: any minor un-intended departure from the approved project protocol and/or Good Clinical Practice (GCP) that does not result in harm to project participants or significantly affect the scientific value of the project data e.g. boxes on consent form ticked rather than initialled; completed consent form misfiled; visit date deviation; single dosing error of recently expired Investigational Medicinal Product (IMP). Repeated non-serious breaches have the potential to be classed as serious breaches dependent on their project impact.

Serious Breach: any departure from the approved project protocol and/or the principles of GCP that has the potential to affect to a significant degree:

- The safety, physical or mental integrity of the project participants; or
- The scientific value of the project.

The judgement on whether a deviation is likely to have a significant impact on the scientific values of the project depends on a variety of factors e.g. trial design, contribution of the data

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to key analysis parameters, impact of excluding data from analysis etc. e.g. multiple randomisation errors; multiple unexplained changes to source data; information sheet and consent form not updated with key safety information in a timely manner.

Urgent Safety Measure (USM): any action taken to protect the participants of a research project against any immediate hazard to their health or safety. USMs can be put in place with immediate effect without any prior authorisations or approvals. Urgent safety issues may relate to the procedures conducted in a research project or to the intervention under investigation.

Waivers: prospective deviations of the approved protocol undertaken knowingly are against GCP and approvals. Within Clinical Trial of Investigational Medicinal Products (CTIMPs) they constitute a deliberate breach of the regulations, are illegal and must not be implemented. Occurrences may constitute a serious breach and be reportable to the competent authority (MHRA in the UK).

2 Purpose

This Standard Operating Procedure (SOP) describes the process for the identification, management and escalation of non-serious and serious breaches of GCP and/or the approved research project protocol. The process for determining whether events constitutes a serious breach and to describe the procedure for implementing and reviewing USMs.

This SOP applies to all STU staff involved with research projects adopted by STU who have delegated responsibilities for managing project deviations and reporting to the Sponsor, REC and the MHRA if a CTIMP (used throughout this document to mean the competent authority).

This SOP may be used for research projects not adopted by STU where staff in Swansea University (SU) or NHS organisations require guidance on managing deviations, breaches or USMs.

3 Background

All research should be undertaken as defined within an the approved protocol according to the UK policy framework for health and social care research (2017). For CTIMPs it is a legal requirement to adhere to the protocol under the Medicines for Human Use (Clinical Trials) Regulations (2004) and the EU Directive when sites in Northern Ireland and the EU are involved.

Deviation from research project protocols or the conditions and principles of GCP often occur in research projects. The majority are technical non-serious breaches which do not result in physical or mental harm to participants, or significantly affect the scientific value or data integrity of the project. Non-serious breaches must be documented with appropriate corrective and preventative actions (CAPAs) taken.

When a non-serious breach of the protocol or GCP is persistently repeated and has the potential to affect to a significant degree the safety, physical or mental integrity of the participants or the scientific value of the project, this may be classed as a serious breach. Serious breaches require reporting to the relevant Research Ethics Committee (REC), R&D departments and if applicable, the MHRA.

To protect the safety of research participants from an immediate hazard to their health and safety, it may be necessary to deviate from the approved protocol. This acceptable deviation is classed as an urgent safety measure (USM), and may relate to the procedures conducted

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in the project or to the intervention under research. All USMs should be notified to the REC, R&D departments and MHRA (if applicable).

4 Roles and Responsibilities

All members of the research team are responsible for reporting any safety issues or suspected deviations or breaches that occur during the research project to the trial office and Sponsor, and for advising if an USM has been implemented.

The **Sponsor** is responsible for recording all breaches and reporting serious breaches in CTIMPs and device studies to the MHRA, and ensuring that appropriate arrangements are in place for reporting when an USM has been implemented. Sponsor must retain oversight of the process when responsibility is delegated.

The **Chief Investigator (CI)** is responsible for ensuring there are mechanisms in place to monitor research activity and identify any deviation with the principles of GCP or the approved project protocol and follow up any USM. The CI must also keep an audit trial of all USMs, non-serious and serious breaches reported to the Sponsor.

The **Trial Manager (TM)** is responsible for ensuring that all USM reports, breach forms, logs, communication and decisions relating to breaches are filed in the Trial Master File. Where delegated, the TM is also responsible for the submission of breach reports and USMs to the ethics committee and MHRA (where applicable), within the designated timescales and disseminating the information to trial sites.

The **STU Manager** is responsible for coordinating the review of breach reports and USMs and the need for a breach assessment team to assess the potential impact of a breach on the project.

A **Breach Assessment Team (BAT)** will facilitate a systematic evaluation of a breach to identify the extent of the breach and devise an appropriate corrective and preventative action (CAPA) plan.

The **Trial Management Group (TMG)** are responsible for reviewing project updates, reported breaches the actioned CAPA.

The **Data Monitoring Committee** (DMC) are responsible for reviewing final collated information relating to serious breaches and USMs and communicating any recommendations to all relevant parties.

5 Procedure

5.1 Identification of non-serious deviations/breaches

Deviations/non-serious breaches may be identified during routine quality control procedures by the trial office, or reported directly from the Principal Investigator (PI) or other site staff.

Deviations/non-serious breaches e.g. missed visit date, may be recorded in the participant notes or Case Report Form and do not require reporting to the sponsor. However, recurrent consistent non-serious breaches from the protocol/GCP may constitute a serious breach if they violate conditions of project approvals or the law.

Any significant deviation from the principles of GCP and/or the protocol at a site which could potentially impact a participant's safety should be recorded on a Deviation, Breaches and USM log (STU-AD-FRM-028) with an explanation and justification of actions taken.

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The site PI must record recurrent, consistent non-serious and potential serious breaches on a Breach Report Form (STU-AD-FRM-029) and report to the trial office within 24 hours of identification.

The CI shall report all potentially serious breaches to the Sponsor as per project requirements.

The TM will ensure that copies of completed logs have been reviewed during a monitoring visit or periodically sent by the site at pre-defined intervals. Site will be instructed to confirm by email if deviations have not been identified during a particular interval.

All breaches and serious breaches should be documented within the Investigator Site File (ISF) of the relevant site using a Deviations, Breaches and USM log (STU-AD-FRM-028).

5.2 Classification of Breaches and Serious Breaches

Any deviation should be considered a potential serious breach where there is a significant impact on:

- participants safety or physical or mental integrity
- the scientific value i.e. completeness, accuracy and/or reliability of the project data

The site PI or delegate must complete a breach report form (STU-AD-FRM-029) and enter the event in a project log (see section 5.1). The TM or CI if appropriate must be notified of any potentially serious breaches as soon as possible and usually no later than 24 hours of site/staff becoming aware.

The CI/TM must notify the Sponsor of a potential breach as soon as possible and usually no later than 24 hours of becoming aware.

5.3 Assessment of deviations/breaches/serious breaches

All identified recurrent, consistent non-serious and potential serious breaches reported to the trial office should be escalated to the STU Manager or delegate.

The STU Manager will undertake an initial assessment of the reported event with the reporting party to establish further action required.

An assessment to determine whether the event should be categorised a serious breach will be coordinated by the STU manager or delegate including consideration of whether the deviation:

- Affects patient safety, confidentiality or data integrity to a significant degree
- Relates to a substantial GCP deviation
- Indicates several, persistent deviations suggesting a systematic failure
- Shows significant failure to comply with required regulations

Where the event appears to meet the criteria of a potential serious breach the STU Manager will coordinate an investigation with the TM, including convening of a Breach Assessment Team (BAT) if required. The outcome of the investigation will be documented in the breach report (STU-AD-FRM-029). When the investigation is complete, the TM must forward the report to Sponsor for final review and authorisation as required per project.

5.4 Breach Assessment Team

When a potential serious breach has been identified the STU Manager or delegate shall facilitate a systematic evaluation of the issue with a Breach Assessment Team. The Team shall comprise the CI and PI (if relevant), sponsor representatives, key members of the research team (e.g. TM, Data Manager) and other experts from within the sponsors organisation or external parties as required.

The Breach Assessment Team (BAT) shall:

- Confirm whether the breach meets criteria for a serious breach or not.

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- Identify which section of GCP or the approved protocol has been breached
- Identify how the reach impacts in trial participants and/or the scientific integrity of the research project.

The BAT shall make a judgement on whether to implement an USM such as a temporary halt to the research project or on specific aspects of the research, pending further investigation as required. The CI or a PI may implement an USM before the BAT conducts its assessment (See section 5.8).

The BAT will work with the CI to identify the extent of the breach and finalise a CAPA plan. The BAT shall agree who needs to be notified of the breach and any follow up actions required. The DMC will receive the BAT report for review and comment.

All records and communication of potential serious breaches shall be retained, including those not deemed serious by a BAT and shall be filed in the relevant Trial master File (TMF) and/or sponsor files as required.

5.5 Escalation of a repeated deviation / breach
When an investigator/site has serious and/or persistent non-serious breach there must be an escalation process which may include:

- Address the deviation through an investigation and resulting CAPA plan.
- Assess the deviation in terms of identifying and reporting them as a serious breach (where applicable)
- Escalate issue with investigators through local management (e.g. R&D offices), to facilitate future compliance
- Trigger an on-site monitoring visit or audit
- Terminate the investigator/sites participation in the project

Any escalation process and resulting decision must be clearly documented in the TMF.

5.6 Reporting Deviations and Serious Breaches
Where a serious breach has been confirmed, it is the responsibility of the Sponsor (or delegate) to notify the REC within 7 calendar days of the matter coming to their attention.

Where delegated, the TM should notify the REC with the Breach Report Form STU-AD-FRM-029 completed with as much information as available.

For CTIMPs, the MHRA should be notified using the current version of the report form found on the MHRA website in the ‘Good practice, inspections and enforcement’ section. This form should be copied to the REC.

Follow up reports should be submitted to the REC and MHRA if actions cannot be fully identified within the initial report.

Full guidance on the reporting process for serious breaches for CTIMPs is available on the MHRA website (see references).

The TM is responsible for ensuring all report forms and correspondence with the REC and MHRA is filed within the TMF. The MHRA and/or REC may enter into a dialogue with the trial office. All verbal conversations should be recorded (preferably by follow up email) and filed in the TMF.

5.7 Ongoing oversight of deviations, violations and serious breaches
Following the start of recruitment, the TM should periodically provide an update on any non-serious and serious breaches at TMG meetings.

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The TMG will review that any required CAPAs are effective and implemented in a timely manner.

Any corresponding comment or actions from the TMG must be documented and filed within the TMF.

5.8 Urgent Safety Measures

5.8.1 Implementation

For all research projects, a research sponsor and CI, PI or other delegated clinically qualified Co-investigator may take appropriate USMs in order to protect a research participant from any immediate hazard to their health and safety. USMs may also be prompted by a DMC following review of the project data. In all instances, USMs may be implemented without prior authorisation from the REC or MHRA (when involved).

Where possible, a site PI should discuss an USM with the CI prior to implementation.

When an USM has been implemented the responsible person must complete an Urgent Safety Measure Notification Form (STU-AD-FRM-030) and email the completed form to the Trial Office immediately, and no later than 24 hours following identification of the USM.

The TM or delegate will immediately ensure that Sponsor, CI and STU Manager have received the USM for review and actioning as required.

Where delegated, the STU Manager in conjunction with the CI, and TM will assess the USM and convene a BAT if required.

5.8.2 Reporting an Urgent Safety Measure

Where delegated from the CI or site, the TM should notify the REC, R&D departments and MHRA (where applicable) of the USM by completing the appropriate documentation.
If the USM relates to research of a pandemic disease, a serious or potential serious risk to human health then the REC and MHRA must be informed as soon as possible. For all other cases the REC and MHRA must be informed no later than 3 calendar days following occurrence.

REC, R&D departments and MHRA should be notified in the form of a substantial amendment or project suspension. The amendment should clearly outline what measures have been taken and the reasons why, including any decisions taken by project committees. An end of trial declaration should be completed where relevant.

The current REC safety report (Non-CTIMP or CTIMP Safety Report Form) should be submitted with details of the USM and, a substantial amendment/end of trial declaration form as appropriate.

For a CTIMP, the MHRA advise phoning their Clinical Trials Unit to discuss the incident with a safety scientist. This initial telephone contact should be followed with written communication (usually via email), the submission of a substantial amendment or suspension/early termination detailing the USM and the reasons for implementation.

Notification to the REC, MHRA and all relevant R&D offices should be completed in parallel.

All research projects which have been suspended due to an USM can only be restarted by submitting a substantial amendment providing evidence that it is safe to restart the research project.

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The TM must inform the sponsor of any USMs and ensure that they receive a copy of all correspondence with the REC, HRA and MHRA, where appropriate.

The TM should inform all participating sites within 24 hours of the USM being implemented detailing all actions to be taken. Sites should be asked to confirm receipt of any documentation and implementation from each PI. Copies of notifications/receipts from sites must be requested and retained in the TMF.

5.9 Safeguarding

Safeguarding practices are most commonly applied to vulnerable adults and young people under the age of 18.

Where the researcher has a particular concern relating to a research participants wellbeing and safety there may be instances where the disclosure of sensitive or confidential information to a third party is necessary. In such instances, the researcher must have clear justification for the disclosure of information and should seek support from the CI, ethics committee and other relevant persons. Decisions taken should be clearly documented.

For further information on Safeguarding, researchers should seek advice from the Research Sponsor and their local safeguarding policy(ies) and the Safeguarding Vulnerable Groups Act (2006). See references for website link.

6 References

- Health Research Authority website (HRA) - http://www.hra.nhs.uk/
- Medicine and Healthcare products Regulatory Agency website (MHRA) - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/services-information
- UK policy framework for health and social care research (2017) - **Error! Hyperlink reference not valid.**https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/
- UK Medicine for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made
- Safeguarding Vulnerable Groups Act 2006 - https://www.legislation.gov.uk/ukpga/2006/47/contents

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

7 Associated Documents

Number	Title	Location
STU-AD-FRM-028	Deviations, Breaches and Urgent Safety Measures Log	Q-Pulse
STU-AD-FRM-029	Breach Reporting Form	Q-Pulse
STU-AD-FRM-030	Urgent Safety Measures Notification Form	Q-Pulse

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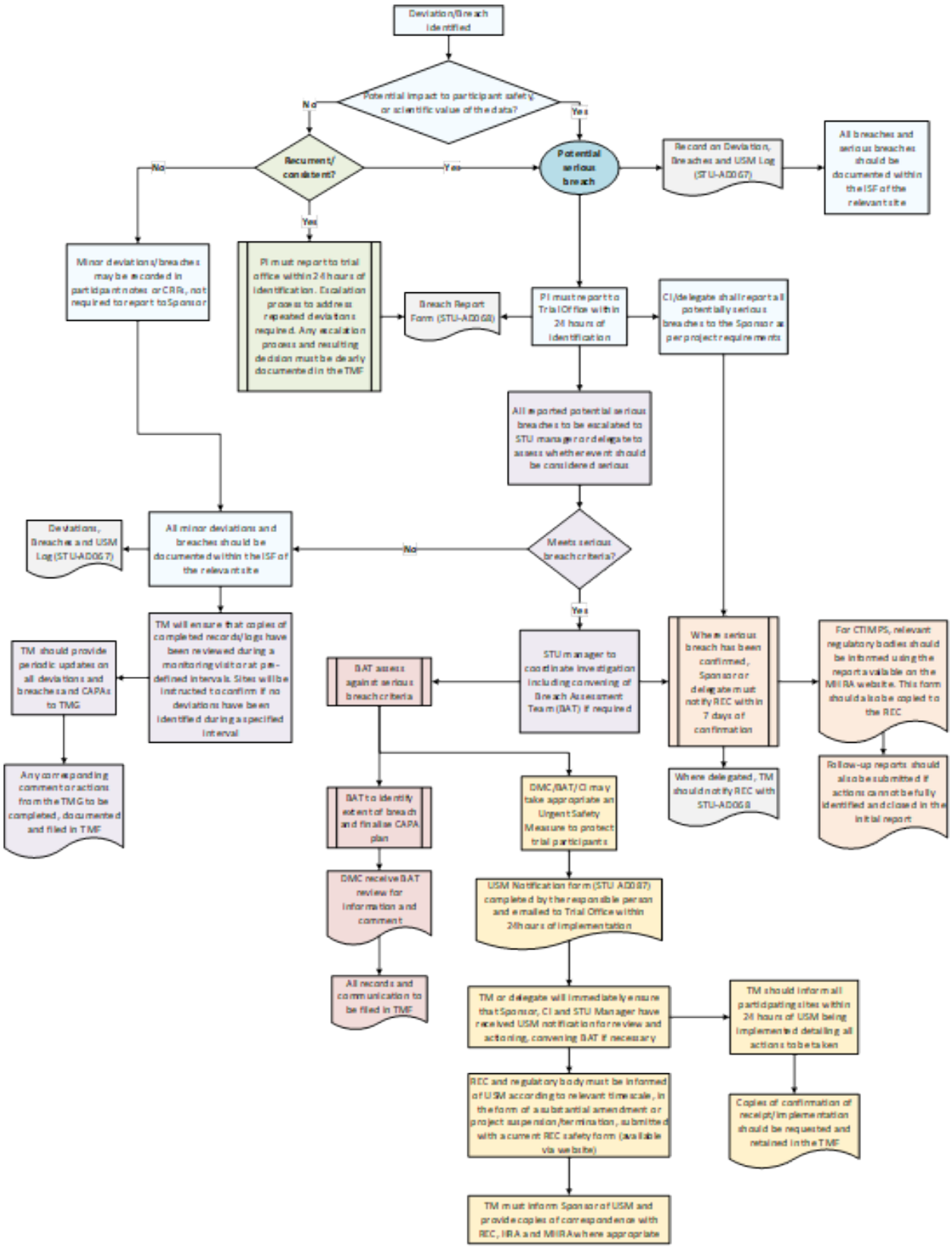
8 Appendices

Appendix 1: Deviations, Breaches and USMs flowchart



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