

## STU-SOP-TM-001 – Standard Operating Procedure on Safety Reporting for Interventional studies including CTIMPs

<b>Version No:</b>	<b>4</b>	<b>Effective Date:</b>	27-Apr-2026
<b>Description of changes:</b>	SOP reviewed in light of clinical trial regulations 2025 and GCP updates. SOP updated to reflect the change of staff roles at STU. Specific references to QPulse as the QMS have been removed. We now only refer to a QMS system.		

List of Abbreviations	
<b>AE</b>	Adverse Event
<b>AR</b>	Adverse Reaction
<b>APR</b>	Annual Progress Reports
<b>CI</b>	Chief Investigator
<b>CRF</b>	Case Report Forms
<b>CTA</b>	Clinical Trial Authorisation
<b>CTIMP</b>	Clinical Trial of an Investigational Medicinal Product
<b>DMC</b>	Data Monitoring and Ethics Committee
<b>DSUR</b>	Development Safety Update Report
<b>GCP</b>	Good Clinical Practice
<b>IB</b>	Investigator Brochure
<b>ICH</b>	International Conference on Harmonisation
<b>ISF</b>	Investigator Site File
<b>MA</b>	Marketing Authorisation
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>MP</b>	Medicinal Product
<b>PI</b>	Principal Investigator
<b>R&amp;D</b>	Research and Development
<b>REC</b>	Research Ethics Committee
<b>RSI</b>	Reference Safety Information
<b>SAE</b>	Serious Adverse Event
<b>SAR</b>	Serious Adverse Reaction
<b>SUSAR</b>	Suspected Unexpected Serious Adverse Reaction
<b>SmPC</b>	Summary of Product Characteristics
<b>SOP</b>	Standard Operating Procedure
<b>STU</b>	Swansea Trials Unit
<b>SU</b>	Swansea University
<b>TM</b>	Trial Manager
<b>TMF</b>	Trial/Project Master File
<b>TMG</b>	Trial Management Group
<b>TSC</b>	Trial Steering Committee

### 1. Purpose and Definitions

This Standard Operating Procedure (SOP) describes the procedure for identifying, recording and reporting an Adverse Event (AE), Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR) principally in Clinical Trials of Investigational Medicinal Products (CTIMPs).

It also describes the procedure for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) via the Medicines and Healthcare products Regulatory Agency (MHRA) ICSR submission online system.

The principles of this SOP may also be used for interventional research projects e.g. involving a medicinal product but not a CTIMP, devices, surgical trials, etc. In such instances the process will be documented in the protocol.

Definitions for assessing an event/reaction type	
<b>Adverse Event (AE)</b>	<p>Any untoward medical occurrence/incident in a participant administered an Investigational Medicinal Product (IMP) or involving an intervention in a research project, including occurrences which are <b>not necessarily caused or related</b> to that product/intervention.</p> <p>An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease.</p>
<b>Adverse Reaction (AR)</b>	<p>Any untoward and unintended response or reaction in a participant administered <b>any dose of</b> IMP or involving an intervention in a research project and is considered as having a reasonable causal relationship to the product or intervention.</p> <p>ARs may be classified as:</p> <p><b>Expected:</b> AR is consistent with the AR profile of the IMP/intervention as listed in the research protocol, Investigator Brochure (IB), or Summary of Product Characteristics (SmPC).</p> <p><b>Unexpected:</b> AR is not consistent with the AR profile expected in the research protocol, IB or SmPC <b>OR</b> the documented AR has occurred at a frequency or severity greater than expected.</p>
<b>Seriousness:</b>  <b>Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)</b>	<p>Defined criteria for seriousness are any AE or reaction in a trial participant at any dose which:</p> <ul style="list-style-type: none"> <li>• Results in death</li> <li>• Is life-threatening (<i>patient was at risk of death at time of event</i>)</li> <li>• Requires hospitalisation (<i>any inpatient admission regardless of length of stay</i>) or prolongation of existing stay in hospital</li> <li>• Results in persistent or significant disability or incapacity</li> <li>• Consists of a congenital abnormality or birth defect</li> <li>• Is an important medical event that may not immediately be life threatening, resulting in hospitalisation or death, but may jeopardise the participant or require intervention to prevent one of the other outcomes listed above</li> </ul> <p>Life threatening, by definition, refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> <p>Medical judgement by the PI/CI or medical delegate should be exercised in deciding whether an AE or AR is serious.</p>
<b>Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	<p>Any AR classed as serious and suspected or definitely caused by the IMP/intervention, but not consistent with the known profile of the IMP/intervention as listed in the IB, SmPC or protocol is termed unexpected and is a Suspected Unexpected Serious Adverse Reaction</p>

	<p>(SUSAR).</p> <p>The SmPC, IB or protocol will include the list of known side effects for each drug in the project. This should be consulted when a SAR occurs to determine expectedness. If the event is not listed, or has occurred in a more serious form, or more frequently than expected, it should be considered a SUSAR. All deaths suspected or definitely related to the IMP/intervention should be considered SUSARs.</p>
<p><b>Definitions for assessing an event/reaction</b></p>	
<p><b>Causality</b></p>	<p>The CI/PI or delegate must make a decision on the relatedness of the event to the IMP/intervention:</p> <p><b>Unrelated:</b> where the AE is not considered to be related to the IMP/intervention.</p> <p><b>Possibly:</b> although a relationship to IMP/intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.</p> <p><b>Probably:</b> the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP/intervention.</p> <p><b>Definitely:</b> the known effects of the intervention/IMP or its therapeutic class, or based on challenge testing, suggest that the IMP/intervention is the most likely cause.</p> <p><i>Note: that neither CI nor Sponsor can downgrade a PI causality assessment, however, upgrading of an event is possible. In the event of differing opinions during assessment, BOTH must be provided on the reports.</i></p>
<p><b>Expectedness</b></p>	<p>Should be assessed based on the trial specific reference safety information (RSI). The RSI for IMP with a marketing authorisation (MA) is section 4.8 of the MHRA approved SmPC. For IMP with no MA, the RSI is the relevant section in the Investigators Brochure (IB). Interventional research projects will have RSI equivalent information detailed in the protocol.</p> <p><i>Note: It is possible to list common expected side effects of an IMP in the protocol and with <b>prior agreement</b> from the Sponsor, MHRA and the REC record these SARs for inclusion in annual reports but exclude them from the normal reporting process and timelines. This also applies to SAEs which are known to be common in an underlying disease e.g. death in cancer.</i></p>
<p><b>Severity</b></p>	<p>For all SAEs/SARs the CI or PI should make an assessment of severity based on their clinical judgement. The assessment should be recorded on the trial SAE form according to the following categories:</p> <p><b>Mild:</b> an event that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with everyday activities</p> <p><b>Moderate:</b> an event that is sufficiently discomforting to interfere with normal everyday activities.</p> <p><b>Severe:</b> an event that prevents normal everyday activities.</p>

	<p><i>Note: The term <b>severe</b> used to describe the intensity of an event or reaction should not be confused with the term <b>serious</b> which is a regulatory term used for trial participant/event outcome. For example, a headache may be severe but not serious, while a minor stroke may be serious but not severe.</i></p>
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<p><b>Individual Case Safety Reports (ICSR) Submissions</b></p>	<p>Electronic reporting of SUSAR's involving IMP to the MHRA via the UK reporting route. This should be within 7 days for fatal and/or life-threatening events and 15 days for all other events.</p> <p><i>Note: Interventional research projects involving a device will have MHRA reporting requirements detailed in the protocol. For CTIMPs including a foreign site additional national requirements will be required and detailed in the protocol.</i></p>
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## 2. Background

This SOP is written in accordance with the applicable Good Clinical Practice (GCP) requirements as outlined in the European Union Regulations, UK guidance and laws and subsequent amendments.

It is the responsibility of the sponsor to ensure that projects comply with the required regulations, even when tasks are delegated. This SOP will detail STU and trial team responsibilities to document oversight and management of safety systems for non-commercial CTIMPs and interventional research.

The guidance for reporting safety events to NHS Research Ethics Committee (REC) projects applies to all projects that have received an NHS REC favourable opinion.

## 3. Roles and Responsibilities

The **Sponsor** is required under laws and regulations to ensure that adverse events are appropriately recorded, reviewed and reported to the Research Ethics Committee (REC) and the MHRA (where appropriate).

The **Chief Investigator (CI)** is usually delegated responsibility for reporting SAEs by the Sponsor, and this will be formally documented in the delegation of responsibilities schedule as issued by the Sponsor.

The **Trial Manager (TM)** is usually delegated responsibility for receiving notification that an adverse event has occurred and ensuring appropriate review, assessment and reporting of the event to relevant parties.

**Swansea Trials Unit (STU)** has responsibility for ensuring that an appropriate assessment process of adverse events is in place, a review has occurred for each event and that SUSARs are reported to the MHRA via the ICSR portal, and other regulators as appropriate. They are also responsible for ensuring that Sponsor, REC and R&D are aware of events as applicable.

The **Principal Investigator (PI)** has responsibility for assessing events that occur and reporting to the CI and trial office as per protocol.

External use of SOP: This SOP and Associated Documents (AD) may be used for research projects not adopted by STU where Swansea University (SU) staff and associated NHS organisations require guidance. In such instances, oversight responsibility for any associated tasks will not be the responsibility of STU.

## 4. Procedure

### 4.1 Protocol Safety Section

The decision on what AEs to record and report should be determined during the protocol development stage and informed by the risk assessment (see STU-SOP-TS-005) usually completed by the Sponsor, STU and CI.

The decision on recording and reporting SAEs (which are a subset of AEs) should also be determined during protocol development particularly in relation to whether any will be recorded as outcomes as well as SAEs.

### 4.2 Identifying an Adverse Event

AEs may be identified by the research team, self-reported by study participants or identified during the assessment of trial outcomes by support departments e.g. haematology, clinical biochemistry or imaging. Where notification of abnormal measurements is not standard clinical practice, the procedure for notifying out of range events to the CI or PI must be documented in the protocol. Case Report Forms (CRFs) should be designed to highlight where data might be out of range and to drive an explicit decision as to whether the data might be clinically significant i.e. an AE/AR.

AEs should be recorded for all study participants following informed consent being obtained, regardless of whether the participant has yet received the IMP/intervention unless there are exceptional circumstances to consider, which have prior agreement of the sponsor and are detailed in the protocol. The protocol must also stipulate when safety reporting ends per participant and the instructions for following up any unresolved AEs until the end of the study where feasible.

All AEs should be recorded by the researchers in the participant medical records. They should also be captured in the participant's AE log (STU-AD-TMP-008). AEs should be recorded and reported within a follow-up period for safety as defined in the protocol. In some trials AEs may not be recorded or only particular AEs will be collated. This will be detailed in the protocol and will require relevant approvals.

### 4.3 Assessment of an Adverse Event

All AEs must be assessed according to the trial protocol and the definitions listed in section 1 of this SOP. The process is outlined in Appendix 1. Further information can be found at <https://www.gov.uk/guidance/clinical-trials-for-medicines-collection-verification-reporting-of-safety-events#reporting-suspected-unexpected-serious-adverse-reactions-susars>.

AEs can be assessed for seriousness by the clinical trial team. If serious, the PI or CI must be notified and decisions made regarding; the severity of the event, the likelihood of the event being related to the IMP/intervention (causality), and likelihood of the event being expected or unexpected (refer to definitions in section 1).

For blinded trials, AEs will be assessed as though the participant was receiving the IMP/intervention and unblinding occurring only if the event is unexpected as per the RSI (see MHRA decision tree for information regarding the need to unblind [https://assets.publishing.service.gov.uk/media/68dac869ef1c2f72bc1e4bc1/fig3\\_unblinding\\_after\\_sars.pdf](https://assets.publishing.service.gov.uk/media/68dac869ef1c2f72bc1e4bc1/fig3_unblinding_after_sars.pdf)). Comparators and placebos are IMPs and any SUSAR associated with these must follow the same reporting requirements as for the test IMP.

#### 4.4 Reporting Procedures for Participating Study Locations

AEs and ARs are not typically reportable to the trial office and are only recorded on CRFs and AE logs for interim review. Reportable AEs and ARs will be defined and the process for reporting them will be detailed in the protocol.

PIs at participating locations must report a SAE/SAR in a study participant within 24 hours of becoming aware of the event, to the trial office as specified in the protocol.

The minimum information required for reporting is detailed in the SAE reporting form (STU-AD-FRM-008). The SAE form should be completed as thoroughly as possible with all available details. Missing information must be provided in a follow up SAE report as soon as available.

Reports should be scanned and attached to an email and sent to the appropriate address. This will usually be to the CI and/or the trial office via the trial specific email address as detailed in the trial protocol.

#### 4.5 Reporting Procedures for Chief Investigators

Following receipt of the SAE/SAR information, the CI should review and assess the report ensuring that causality, expectedness and seriousness have been determined in line with the RSI.

All SAEs considered to be related to the IMP, and not consistent with the information detailed in the RSI will be treated as SUSARs and subject to expedited reporting to the MHRA and REC within 7 or 15 days depending on the type of event (see definition in Section 1).

If the CI disputes the assessment made by the PI an upgrade of the event is permitted, however, a downgrading of an event is not possible. Under such circumstances both assessments should be noted and forward if expedited reporting of a SUSAR to the MHRA and REC is required, abiding by the regulatory timelines of 7 days – fatal and life threatening events; 15 days – all other events. Where relevant the protocol may allow for reporting SUSARs in a timeframe that reflects the urgency of the action required.

Non-CTIMP interventional research reporting will follow the above reporting format where possible (excluding MHRA procedures).

**Where** SAEs/SARs are expected, the protocol should ideally list them and not require expedited reporting. They should still be added to the AE log (STU-AD-TMP-008) and an SAE report completed as per Section 4.4. The timeline for submission of these will vary depending on the purpose of the trial, toxicity and efficacy endpoints.

It is the CI responsibility to forward any directly received SAE reporting forms from participating locations to STU who will collate the reports on behalf of the Sponsor, REC, MHRA (if required) and oversight committees.

#### **4.6 ICSR registration (CTIMPs only)**

The Sponsor must register as an organisation to the ICSR Submissions portal (see <https://mhra-transfer.sharefile.com/share/view/s0dfa3aeb46c45c18> for guidance). They will allocate access to at least the CI, TM and STU representative to allow submission of SUSARs for an individual CTIMP.

#### **4.7 Safety Reporting for non-CTIMPs**

For all other studies, including clinical investigations of medical devices, only reports of SAEs that are:

- related to the study (i.e. they resulted from administration of any of the research procedures) and
- unexpected (i.e. not listed in the protocol as an expected occurrence)

should be emailed to the REC using the [Non-CTIMP safety report to REC form](#) on the HRA website (<https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/>).

These should be sent within 15 days of the CI becoming aware of the event. Reports of SAEs in double-blind trials should be unblinded. There is no requirement for annual safety reports.

#### **4.8 Multicentre Trial SUSARs**

It is the CIs responsibility to alert other investigators that a SUSAR has occurred. This will usually be via email safety alerts, with the procedure and timelines detailed in the protocol.

#### **4.9 Pregnancy Reporting**

If required by the protocol, the CI or PI must collect pregnancy information for female trial participants who become pregnant, or female partners of male trial participants who become pregnant.

The CI, PI or delegated Clinician should record the information on the trial pregnancy form as per the Pregnancy Reporting template (STU-AD-FRM-009) and send this to the trial office by trial specific email within 14 days of being made aware of the event.

Any pregnancy that occurs in a trial participant or a trial participant's partner should be followed to outcome. It may be necessary to monitor the development of the newborn for an appropriate period post-delivery, typically 12 months. This requirement must be specified in the trial protocol.

If the female participant or female partner of a male participant does not agree to this information being collected their wishes should be respected and a note to that effect made in the clinical research form and the medical records.

Pregnancy ONLY becomes an SAE/SAR/SUSAR if the mother or the foetus suffers any complications of pregnancy or childbirth, or any abnormality which fulfils any serious criteria (refer to the definitions in section 1). The PI or CI must assess the event for causality and relatedness to the IMP/intervention.

STU will forward reports to Sponsor as agreed for the trial.

#### 4.10 Aggregate Reporting

The TM will be responsible for compiling reports of aggregated safety data for regular review by the Trial Management Group, sponsor and oversight committees to identify patterns of events not obvious in isolation i.e. signal management. This includes all events including those prior to the intervention being given.

Formal reporting of events for CTIMPs involve the submission of Development Safety Update Reports (DSURs). Please refer to STU-SOP-TM-007.

## 5. References

- Health Research Authority website (HRA) - <http://www.hra.nhs.uk/>
- Medicine and Healthcare products Regulatory Agency website (MHRA) - <https://www.gov.uk/guidance/clinical-trials-for-medicines-collection-verification-reporting-of-safety-events>
- UK policy framework for health and social care research (2017) - <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 2025 - <https://www.legislation.gov.uk/uksi/2025/538/contents>
- International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) E6 R3 Guideline - [https://database.ich.org/sites/default/files/ICH\\_E6%28R3%29\\_Step4\\_FinalGuideline\\_2025\\_0106.pdf](https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf)

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

## 6. Associated Documents

Number	Title	Location
STU-AD-TMP-008	Adverse Event Log Template	QMS
STU-AD-FRM-008	SAE Reporting Form	QMS
STU-AD-FRM-009	Pregnancy Reporting Form	QMS

## 7. Appendices

### Appendix 1: Decision Framework for Assessment of Adverse Events by Investigators and Research Personnel.

