STU-SOP-TM-001 – Standard Operating Procedure on *Safety Reporting for CTIMPs*

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, device, surgical etc. In such instances the process will be documented in the protocol.

Definitions	
Adverse Event (AE)	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 **not necessarily caused or related** to that product/intervention. An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease.
Adverse Reaction (AR)	Any untoward and unintended response or reaction in a participant administered **any dose of** IMP or involving an intervention in a research project and is considered as having a reasonable causal relationship to the product or intervention. ARs may be classified as: **Expected**: 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). **Unexpected**: AR is not consistent with the AR profile expected in the research protocol, IB or SmPC **OR** the documented AR has occurred at a frequency or severity greater than expected.
Causality	The CI/PI or delegate must make a decision on the relatedness of the event to the IMP/intervention: **Unrelated**: where the AE is not considered to be related to the IMP/ intervention. **Possibly**: 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. **Probably**: the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP/intervention.

	Definitely: 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. *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.*
Individual Case Safety Reports (ICSR) Submissions	Electronic reporting of SUSAR's involving IMP to the Medicines and Healthcare products Regulatory Agency (MHRA) via the UK reporting route. This should be within 7 days – fatal and life threatening events; 15 days – all other events. *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.*
Expectedness	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 Summary of Product Characteristics (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. *Note: It is possible to list common expected side effects of an IMP in the protocol and with **prior agreement** 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.*
Seriousness: Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Defined criteria for seriousness is any AE or reaction in a trial participant at any dose which: • Results in death • Is life-threatening *(patient was at risk of death at time of event)* • Requires hospitalisation *(any inpatient admission regardless of length of stay)* or prolongation of existing stay in hospital • Results in persistent or significant disability or incapacity • Consists of a congenital abnormality or birth defect • 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 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. Medical judgement by the PI/CI or medical delegate should be exercised in deciding whether an AE or AR is serious.
Severity	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:

	Mild: an event that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with everyday activities **Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities. **Severe:** an event that prevents normal everyday activities. *Note: The term '**severe'** used to describe the intensity of an event or reaction should not be confused with the term '**serious**' 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*.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	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 (SUSAR). 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.

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 a NHS Research Ethics Committee (REC) projects applies to all projects that have received a NHS REC favourable opinion.

3. Roles and Responsibilities

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).

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.

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 portal, and other regulators as appropriate. They are also responsible for ensuring that Sponsor, REC and R&D are aware of events as applicable.

Principal Investigator (PI) at sites 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 trials protocol development and informed by the risk assessment 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 rather than as SAEs.

4.2 Identifying an Adverse Event

AEs may be identified by the research team, self-reported by trial 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.

AEs should be recorded for all trial participants following informed consent being obtained, regardless of whether the participant has yet received the investigational medicinal product, unless there are exceptional circumstances to consider, which have prior agreement of the sponsor and are detailed in the protocol.

All AEs should be recorded by the researchers in the participant medical records. They should also be captured in the Case Report Form (CRF) via 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.

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.

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.

4.4 Reporting Procedures for Participating Sites

PI's at participating sites must report a SAE in a trial participant within 24 hours of becoming aware of the event, to the trial office as specified in the trial 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 report as soon as available.

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

4.5 Reporting Procedures for Chief Investigators

Following receipt of the SAE 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 event.

In the event of the CI disputing 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.

Interventional research reporting will follow the above reporting format. MHRA requirements for interventional research will be detailed in the protocol.

Expected SAEs/SARs should only be reported to STU on the AE log (STU-AD-TMP-008) as per protocol. 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 sites to STU who will collate the reports on behalf of the Sponsor.

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

4.6 ICSR registration (CTIMPs only)

The Sponsor must register as an organisation to the ICSR Submissions portal. They will allocate access to at least the CI, TM and STU Manager to allow submission of SUSARs for an individual CTIMP.

4.7 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.

4.8 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 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. 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.

5. 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) - 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
- International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) E6 Guideline - http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

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	Serious/Adverse Event Log Template	Q-Pulse
STU-AD-FRM-008	SAE Reporting Form	Q-Pulse
STU-AD-FRM-009	Pregnancy Reporting Form	Q-Pulse

7. Abbreviations

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

8. Appendices

Appendix 1: Document History

Version No:	**3**	**Effective Date:**	25-Mar-2024
Description of changes:	Update of procedures: Update UK procedure for reporting SUSARs. Moved to SOP Template v5.		

Appendix 2: Decision Framework for Assessment of Adverse Events by Investigators and Research Personnel.