STANDARD OPERATING PROCEDURE FOR IDENTIFYING, ASSESSING AND REPORTING ADVERSE EVENTS FOR CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS (CTIMPs)

SOP NUMBER:	TASC SOP011 v16
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1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for identifying, assessing and reporting Adverse Events (AEs), including Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)) occurring in Clinical Trials of Investigational Medicinal Products (CTIMPs) which are sponsored or co-sponsored by the University of Dundee (UoD) and/or NHS Tayside (NHST) where NHST has been delegated the responsibility for Pharmacovigilance (PV). This document also describes the procedure for Pregnancy reporting.

2. SCOPE

The Sponsor pharmacovigilance procedure complies with the requirements of the Medicines for Human Use (Clinical Trial) Regulations 2004 and the European Pharmacovigilance Regulations (effective 2012) and subsequent amendments.

Pharmacovigilance may be delegated to a third party, but the process and reporting duties must be agreed between the Sponsor and third party before the trial commences with the responsibilities clearly documented.

This SOP applies to members of staff associated with and managing CTIMPs that are sponsored or co-sponsored by the UoD or NHST.

3. RESPONSIBILITIES

Investigator (Chief Investigator (CI), Principal Investigator (PI)) or delegate:

- to immediately report SAEs and certain non-serious adverse events and/or laboratory abnormalities to the Sponsor via ***Tayside Pharmacovigilance System***.
- must collect pregnancy information for female participants or female partners of male participants and report to TASC Pharmacovigilance.

Sponsor (TASC Pharmacovigilance):

- to keep a record of all the notified SAEs, SARs and SUSARs.
- to notify SUSARs to the licensing authorities (Medicines and Healthcare products Regulatory Agency (MHRA) or other) which approved the study and inform the CI.

- To keep a record of all the notified pregnancy information.

4. PROCEDURE

4.1 Identifying, Classifying and Assessing AEs, ARs, SAEs and SARs

The protocol should define how AEs and ARs will be identified, recorded, and reported and also the time period.

AEs will be recorded from participant's consent to take part in the trial until their last trial visit, unless specified in the protocol.

Information on AEs should be recorded in source records and added in the AE Log (Doc Ref 086) and/or Case Report Form (CRF) (if applicable).

For the classification of AEs, please see Table 1 below:

Table 1

Adverse Event (AE): Any untoward medical occurrence in a consented participant which is not necessarily caused by or related to a medicinal product.
Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. An untoward and unintended response to a Non-Investigational Medicinal Product (NIMP) should be recorded as an AR. This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected SAR: SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not. Any adverse event, adverse reaction, or unexpected adverse reaction respectively that: - Results in death. - Is life threatening. - Requires hospitalisation or prolongation of existing hospitalisation. - Results in persistent or significant disability or incapacity. - Results in a congenital anomaly or birth defect. - Any important medical events which jeopardise the participant or require intervention to prevent one of the above.

"Important medical events" may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. The term "life threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected SAR: A serious adverse reaction, the nature and severity of which is not consistent with the reference safety information about the medicinal product as listed in the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC), as specified in the protocol.

4.1.1 Assessment of AEs

Reporting requirements for AEs in clinical trials are dependent on certain assessments, including seriousness and causality.

Seriousness and causality must always be assessed by a medically qualified doctor (usually the Investigator) who has been delegated this task on the Delegation Log.

For randomised, double-blind trials, AEs should be assessed as though the trial participant was taking the active study drug.

4.1.2 Seriousness Assessment

The Investigator should assess the AE based on the criteria defining SAEs and SARs (Table 1).

4.1.3 Severity Assessment

Severity refers to the intensity of the event/reaction and is often classified by its effect on the everyday living of the participant as mild, moderate or severe.

The Investigator should assess the severity of all AEs using the following definitions:

- **Mild**: a reaction that is easily tolerated by the trial participant, causing minimal discomfort, and not interfering with everyday activities.
- **Moderate**: a reaction that is sufficiently discomforting to interfere with normal everyday activities and may warrant intervention.
- **Severe**: a reaction that prevents normal everyday activities or significantly affects clinical status and usually warrants intervention.

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

4.1.4 Causality Assessment

The Investigator should assess the extent to which it is believed that the event may be related to the study drug, using the following definitions:

- **Unrelated**: where the AE is not considered to be related to the study drug.
- **Possibly**: although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication, or temporal relationship makes other explanations more likely. Information on drug withdrawal may be lacking or unclear.
- **Probably**: the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Information on drug withdrawal may be available and if so, the observed response to study drug withdrawal is considered clinically reasonable.
- **Definitely**: the known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. Information on drug withdrawal is usually available and the observed response to study drug withdrawal is considered clinically reasonable and has a plausible temporal relationship to study drug exposure.

All AEs judged to have a suspected causal relationship (i.e., possibly, probably, or definitely) with the IMP will be considered as related to the IMP.

If the causality assessment is missing or not known, the event will be treated as related until informed otherwise, and the Sponsor will follow up with Investigators to obtain a causality assessment before the reporting deadline.

Note: The assessment of causality made by the Investigator cannot be downgraded by either the Chief Investigator or the Sponsor. In the case of a difference of opinion, both assessments should be recorded.

4.1.5 Expectedness Assessment

In case an SAE/SAR is judged to be related to the study drug, the Sponsor (Medical Reviewer) is required to assess expectedness based on the product information documented in the Reference Safety Information (RSI) located in the IB or the Summary of Product Characteristics (SmPC), whichever is being used for that trial. Please refer to TASC SOP on RSI and the assessment of Expectedness.

4.1.6 Reporting safety for NIMPs

An untoward and unintended response to a NIMP will be recorded as an AR.

The reporting rules for the IMP apply if any AE is suspected to be related to an interaction between the IMP and the NIMP.

Where the AE may be linked to either the IMP or NIMP but cannot be attributed to only one of these - this will be considered an AR.

The Investigator will take appropriate actions if any adverse reaction associated with the NIMP is likely to affect the safety of the trial participants (please refer to TASC SOP on Urgent safety measures).

4.2 Reporting SAEs, SARs and Follow-ups by the Investigator to Sponsor

See Appendix 1: Adverse Events Reporting Flowchart for a CTIMP

All immediately reportable SAEs/SARs must be reported to Sponsor using the ***Tayside Pharmacovigilance System***, within 24 hours of the Investigator or delegate becoming aware of the event, except those that the study protocol identifies as not requiring immediate reporting.

Members of study teams with delegated function of safety reporting, must be fully trained on the Tayside Pharmacovigilance System, this can be requested by emailing tay.pharmacovigilance@nhs.scot.

Important Note:
In case of accessibility/system issues when reporting SAE/SAR on the *Tayside Pharmacovigilance System*, the CI/PI or delegate should contact TASC PV monitor by emailing tay.pharmacovigilance@nhs.scot

Certain SAEs/SARs could be deemed to be exempt from immediate reporting to the Sponsor. This decision has to be clearly justified in the protocol. SAEs/SARs that are exempted from immediate reporting to Sponsor should be recorded on the ***Tayside Pharmacovigilance System***.

Unless otherwise stated in the protocol, all SAEs/SARs must be followed up, where feasible, until completion (resolution or death of the participant). Otherwise, the follow-up will be up to 30 days from last visit for that participant. Follow-up reports are submitted through ***Tayside Pharmacovigilance System.***

Copies of all SAE reports recorded on the ***Tayside Pharmacovigilance System*** must be retained by the Investigator in the Trial Master File (TMF) or Investigator Site File (ISF), as applicable.

The information recorded on the ***Tayside Pharmacovigilance System*** and clinical database should match and will be reconciled prior to database lock.

4.2.1 Medical Dictionary for Regulatory Activities (MedDRA) coding

The Investigator will make every effort to include the relevant preferred term (PT) for the event diagnosis when reporting SAEs.

Any risk-proportionate and justified adaptions to coding expectations should be justified to Sponsor.

For reporting SUSARs to the licensing authority, terms must be coded to the PT level. If the investigator has included a term that does not directly match to a MedDRA PT then both the MedDRA PT and the verbatim term will be included in the SUSAR report.

4.2.1 Expedited reporting of SUSARs by the Sponsor

The Sponsor is responsible for reporting SUSARs to the licensing authority (MHRA or other) which approved the study.

The timeframe for reporting is the following:

- SUSARs that are fatal or life-threatening must be reported within 7 calendar days of Sponsor's receipt of the Investigator's report.
- Other non-fatal or life-threatening SUSARs must be reported within 15 calendar days.

The day of receipt by Sponsor of the information (either initial notification or follow-up) is assigned Day 0.

Only unblinded SUSARs should be reported by the Sponsor. Investigators should only receive blinded information unless unblinding is necessary for safety reasons. All paperwork related to unblinded SUSARs should be filed in a sealed envelope in the Sponsor file but not held in the TMF.

The Sponsor will inform Investigators of SUSARs that occur in relation to an IMP used in trials in which they are involved, in a timeframe that reflects the urgency of any required actions.

The Investigator must review the information provided by Sponsor and act upon it if appropriate. Copies of such SUSAR reports must be kept in the TMF or ISF, as applicable.

The Sponsor can delegate these Pharmacovigilance tasks to National Coordinator centres or third parties, as appropriate.

4.3 Pregnancy Reporting

The Investigator must collect pregnancy information for female trial participants or female partners of male trial participants who become pregnant while participating in a study. The Investigator should record the information on a Pregnancy Notification Form (Doc Ref 058a) and send this to Sponsor within 14 days of being made aware of the pregnancy by email to tay.pharmacovigilance@nhs.scot.

If applicable, informed consent should be obtained from the participant or pregnant partners of trial participants. Any pregnancy that occurs in a trial participant or a trial participant's partner during a trial should be followed to outcome (Doc Ref 058b).

5. ABBREVIATIONS & DEFINITIONS

AE	Adverse Event
AR	Adverse Reaction

CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-Investigational Medicinal Product
NHST	National Health Service Tayside
PI	Principal Investigator
PV	Pharmacovigilance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
UoD	University of Dundee

6. ASSOCIATED DOCUMENTS & REFERENCES

Doc Ref 058a: Pregnancy Notification Form
Doc Ref 058b: Pregnancy Follow Up Form
Doc Ref 086: Adverse Event Log

7. DOCUMENT HISTORY

History prior to 2021 is in the archived SOPs available from TASC Quality Assurance Dept.

Version Number:	Reviewed By (Job Title):	Effective Date:	Details of editions made:
13	Heather Barclay (Pharmacovigilance Monitor)	17/02/2022	Expectedness assessment changed to being a sponsor only responsibility. SAE flowcharts have had section references removed. Historic sections removed and sections renumbered.
14	Joana Rocha (Pharmacovigilance Monitor)	26/06/2023	Change to new Tayside Pharmacovigilance System for SAE reporting. RSI information moved to new Doc Ref 129. SOP title changed from Clinical Research to CTIMPs.

15	Joana Rocha (Pharmacovigilance Monitor)	26/06/2025	Updated SOP title and AE definition. Removed USM procedure and REC reporting requirements. Updated vocabulary as per new ICH E6 R3 guidelines and CT (Amendment) Regulations 2024.
16	Joana Rocha (Pharmacovigilance Monitor)	28/04/2026	Updated in accordance with the new Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

8. APPROVALS

Approved by:	**Date:**
Dr Steve McSwiggan, Senior R&D Manager NHS Tayside	30 Mar 2026
Dr Valerie Godfrey, TASC Quality Assurance Manager, on behalf of TASC Clinical Research Guidelines Committee	27 Mar 2026

Appendix 1: Adverse Events Reporting Flowchart for a CTIMP