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

SOP NUMBER:	TASC SOP011 v14
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1. PURPOSE

This document describes the procedure for identifying, assessing and reporting Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in Clinical Research Trials 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. It 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 research trials that are sponsored or co-sponsored by the UoD or NHST.

3. RESPONSIBILITIES

Sponsor refers to TASC Pharmacovigilance (tay.pharmacovigilance@nhs.scot).

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

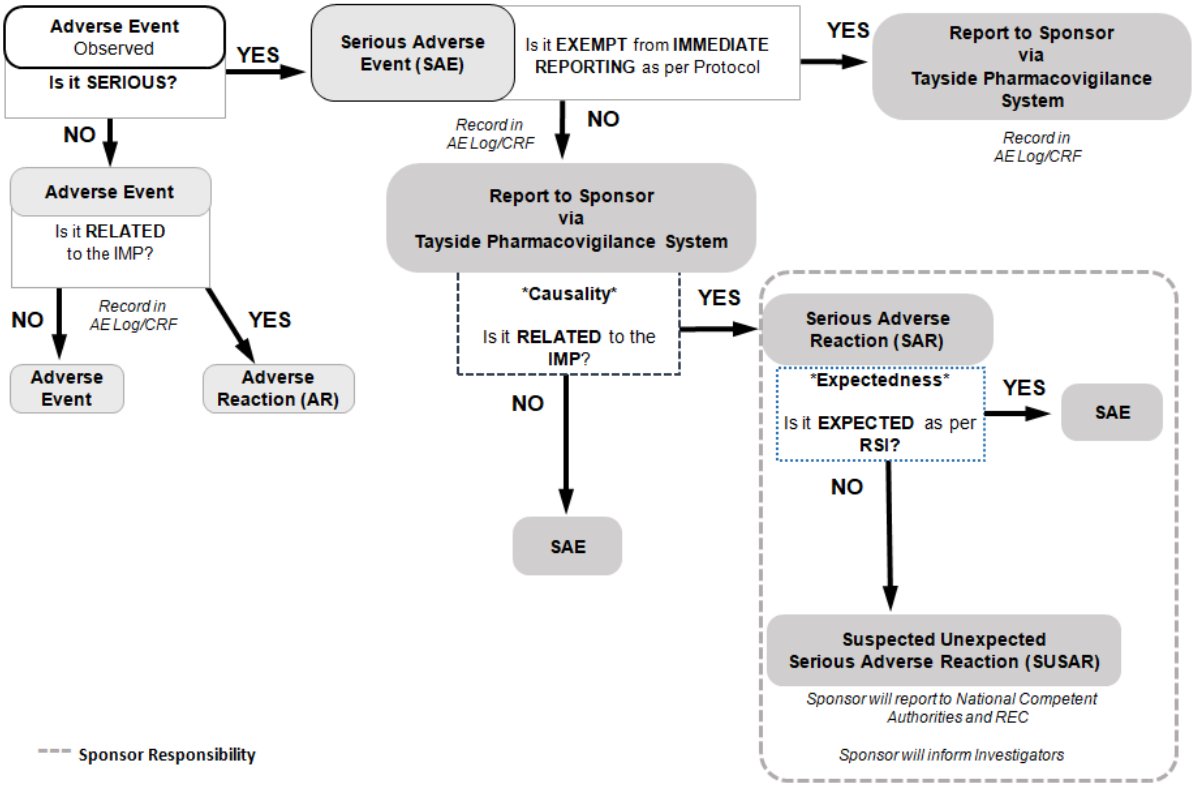
- to immediately report SAEs and certain non-serious adverse events and/or laboratory abnormalities to the Sponsor via ***Tayside Pharmacovigilance System***.

Sponsor:

- to keep a record of all the notified serious adverse events.
- moreover, Sponsor must notify SUSARs to the national competent authorities (MHRA), Research Ethics Committees (REC) and inform the Chief Investigators.

4. PROCEDURE

Adverse Events Reporting Flowchart for a Clinical Trial of an Investigational Medicinal Product (CTIMP)



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 documents 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:

Table1

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR):

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that participant.
Serious Adverse Event (AE), Serious Adverse Reaction (SAR) or Unexpected SAR: 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. - Consist of a congenital anomaly or birth defect. - Any important medical events which jeopardise the subject 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 serious.
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

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.

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 Investigational Medicinal Product (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.

Any AE which is likely to be related to an interaction between the IMP and the Non-Investigational Medicinal Product (NIMP) or where the AE may be linked to either the IMP or NIMP but cannot be attributed to only one of these must be considered as an AR.

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 (clinical reviewer) is required to assess expectedness based on the product information documented in the Reference Safety Information (RSI) located in Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC), whichever is being used for that trial. Refer to Doc Ref 109 for further information on RSI.

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

All immediately reportable SAEs/SARs must be reported to Sponsor using the ***Tayside Pharmacovigilance System***, within 24 hours of becoming aware of the event.

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 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).

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

4.2.1 Expedited reporting of SUSARs by the Sponsor

The Sponsor is responsible for reporting SUSARs to the National Competent Authorities (MHRA or other) which approved the study and to the Research Ethics Committee (REC) which provided a favourable ethical opinion.

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

The Sponsor is required to inform all Investigators, in a timely manner, of SUSARs that occur in relation to an IMP used in trials in which they are involved.

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.

Investigators and Sponsor are encouraged to report unexpected serious adverse reactions related to non-IMPs that are marketed medicinal products, to competent authorities or marketing authorisation holders.

Reports sent to an Investigator regarding SUSARs from other trials of the same medicinal product must be reviewed by the Investigator and acted upon if appropriate. Copies of such SUSAR reports must be kept in the TMF or ISF.

4.2.2 Urgent Safety Measures

The Sponsor and Investigator may take appropriate urgent safety measures to protect the participants of a CTIMP against any immediate hazard to their health or safety.
The Investigator must inform Sponsor of any urgent safety measures implemented.

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

For female partners of male trial participants who become pregnant while participating in a study, consent should be obtained to follow up the pregnancy. 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
MHRA	Medicines and Healthcare products Regulatory Agency

NIMP	Non-Investigational Medicinal Product
NHST	NHS Tayside
REC	Research Ethics Committee
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
Doc Ref 109: Reference Safety Information and the Assessment of Expectedness of Serious Adverse Reactions in Clinical Trials of Investigational Medicinal Products (CTIMP)

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 109. SOP title changed from Clinical Research to CTIMPs.

8. APPROVALS

Approved by:	Date:
Dr Valerie Godfrey, TASC Quality Assurance Manager, on behalf of TASC Clinical Research Guidelines Committee	23 June 2023