UNIVERSITY OF LEICESTER

Research Governance Office Sponsorship Standard Operating Procedures

Processing and reporting safety events for trials

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1.0 Introduction and Scope

The Medicines for Human Use (Clinical Trials) Regulations 2025, ICH GCP E6(R3) and the UK Policy Framework for Health and Social Care Research 2017 set out specific requirements for safety reporting.

This standard operating procedure (SOP) describes the requirements for identifying, documenting and reporting of safety events. This SOP applies to any research (referred to as 'trial' hereafter) sponsored by the UoL with the exception of non-CE marked medical device trials which is detailed in SOP 1043.

2.0 Definitions

These are the standard definitions as per the Medicines for Human Use Clinical Trials Regulations 2025. The National Institute for Health and Care Research (NIHR) has produced a decision tree to help categorise events. For the purposes of this SOP, all definitions of Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Adverse Reactions (SARs) and related terms described below apply to all trials. References in regulatory definitions to 'administration of the investigational product' should be interpreted as applying to any trial intervention or procedure.

2.1 Adverse Event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with any intervention conducted due to the participant participation in the clinical trial, even if not associated to a medicinal product, should also be considered as an AE.

2.2 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. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

An untoward and unintended response to a non-IMP should be recorded as an AR.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

2.3 Adverse Event of Special Interest (AESI)

AESI are not defined within the UK Clinical Trial Regulations but may be considered as a subset of events of scientific or medic concern for the particular product or class of products that require additional reporting. AESI can be serious or non-serious, and may include events that are potential precursors for more serious medical conditions in susceptible individuals. Such events should be described in the Protocol, and instructions provided for investigators as to how and when they should be reported and to whom.

2.4 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or unexpected Serious Adverse Reaction (SUSAR)

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/incapacity, or
- is a congenital anomaly/birth defect
- Other serious important medical event

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this 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.

Medical and scientific judgement should be exercised in deciding whether an event is ‘serious’ in accordance with these criteria.

SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not.

Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events (also referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition.

*In general, hospitalisation means that the participant has been admitted to the hospital for inpatient care, for example to an inpatient ward or to an emergency department for observation and/or treatment (usually involving at least an overnight stay), that would not have been appropriate in the physician’s office or outpatient setting. The protocol should clarify what is considered as hospitalisation in the context of the trial setting since this may vary depending on the overall risk assessment for the trial. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is generally not considered an SAE.

2.5 Unexpected Adverse Reaction

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in either (a) or (b) below.

(a) in the case of a product with a marketing authorization, in the summary of product characteristics (SmPC), or equivalent document, for that product.

(b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

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

For serious adverse reactions and determination of expectedness the version of the RSI at the moment of occurrence of the event applies, not the RSI at the time of case receipt by the sponsor.

3.0 Adverse Event Recording and Reporting

3.1 AE/AR

AE/ARs, whether serious or not, should be documented in the case report form (CRF), trial database and in the participants medical records (where appropriate and as per protocol).

There are no requirements to report AE/ARs to the Research Governance Office (RGO) or regulatory agencies unless they are identified in the protocol as critical to evaluations of the safety of the trial. AE/ARs should be observed to ensure that they do not escalate to a SAE/SAR.

3.2 AESI/SAE/SAR/SUSAR

The Principal Investigator (PI) (or delegate) is responsible for reporting all AESI, SAEs, SARs or SUSARs, and follow-up information, to the RGO via rgosponsor@le.ac.uk immediately and within 24 hours of the research team becoming aware of the event using the SAE Reporting Form (Appendix 8 or 9). Further updates should be provided where all the required information is not available at the time of the initial report and or the event has not yet resolved/stabilised.

SAE reporting forms may be completed and submitted by any member of the research location team who has been delegated the tasks on the Delegation of Activities (DoA) log. However, the assessment of causality must only be completed by the PI or a delegated medic (see Section 3.3). Reporting should not be delayed due to missing information, instead additional information, including the causality assessment, may be provided in amended or follow-up reports.

The reporting form and any supporting documents or correspondence must not contain any participant identifiable information.

All documentation must be filed in the relevant section of the Investigator Site File (ISF), with copies in the TMF. It is recommended an overview of all SAEs occurring at a research location are recorded on a serious adverse event listing table (Appendix 13) and filed in the ISF and TMF.

All events should be followed up until resolution/stabilisation. CRFs and/or the trial database must be updated to record outcomes.

For trials in which a pharmaceutical company requires information beyond what is captured in the SAE Reporting Form, a trial-specific cover sheet may be used. An adaptable template is available in Appendix 7. This cover sheet must be approved by the pharmaceutical company and the RGO prior to use.

3.3 Causality assessment, review and sign-off of SAE reporting forms

Causality refers to whether the event is likely to be related to the trial intervention or a trial procedure. The PI or another medically qualified delegate(s), is responsible for assessing causality.

In some trials it may be appropriate for the causality assessment to be performed by a non-medical investigator where it falls within their normal clinical remit (e.g., nurse prescribers); otherwise, or where the intervention requires additional medical oversight, causality must be delegated to the doctor or dentist on the trial team. In all instances, prior agreement must be provided by the RGO.

3.4 Protocol adaptations

A risk adapted approach to safety reporting may be applied. Such adaptations must be fully justified within the Protocol, and be approved by Sponsor, the MHRA and Research Ethics Committee (REC), as applicable.

4.0 RGO Adverse Event Processing

The below outlines the process followed by the RGO. Where safety reporting/processing (i.e., Pharmacovigilance) is delegated to a 3rd party (i.e., CTU, Service Provider) this must be detailed in the protocol and risk assessment. Where applicable, a contract with a safety data exchange agreement must be in place.

4.1 Receipt of SAE Reports – All trials

1. The RGO will review SAE reports, complete MedDRA coding and expectedness assessments (where applicable), and issue an acknowledgement within 7 days.
2. Where required, requests for amendments, clarifications and missing information will be issued and responses are required within 7 days of the RGO request.
3. Follow-up reports are required within 28 days of the RGO request.
4. The SAE will remain open until all required safety reporting information has been obtained. Once achieved, the SAE will be marked as closed.
5. The RGO will complete any onward reporting as per the Safety Data Exchange Agreement/agreed process.

Note:

- Response times may differ where information/action is required for expedited reporting.
- There may be situations where additional information is dependent on external processes or investigations that could take an extended period to conclude. In these circumstances, routine follow-up requests will not continue according to the usual timelines. Instead, the research team will be expected to provide an update as soon as any new information becomes available, and no later than 24 hours after becoming aware of it. The RGO may periodically check in with the site to confirm whether any developments have occurred.

The RGO maintain a register of all SAEs and retain copies of all reports and associated correspondence. Monthly line listings are prepared for review by the Director of R&I. Fatal events and those related to the IMP/device/intervention may be expedited to the Director of R&I and/or the insurance team as relevant.

4.2 MedDRA Coding – CTIMPs

The RGO will use the latest MedDRA version to code all CTIMP SAEs. The Preferred Term (PT) and corresponding System Organ Class (SOC) will be identified for reporting purposes. Two representatives from the RGO will independently conduct the MedDRA coding; any discrepancies in the selected PT will be discussed, and an Investigator opinion may be sought when required.

Where the receipt of follow-up information alters the diagnosis of the event, the MedDRA coding process will be repeated.

The MedDRA coding process, including the SoC, PT, MedDRA version used, date of coding, and reviewer details, will be documented in the Sponsor SAE database. For the purpose of the Development Safety Update Reports (DSUR – see section 10.0, the PT will be shared with the researchers as part of the email response to the SAE.

4.3 Expectedness Assessment – All trials

Expectedness assessments are required when the event has been deemed as being causally related to a participant's involvement in a trial.

CTIMPs:

The expectedness assessment will be performed against the version of the Reference Safety Information (RSI), located in either the IB or SmPC, that was approved at the time the event occurred.

The outcome of the expectedness assessment (expected or unexpected) and the source of RSI will be recorded in the Sponsor SAE database. Where the receipt of follow-up information alters the diagnosis of the event, the expectedness assessments will be repeated.

Unless otherwise agreed, the RGO is responsible for assessing expectedness for CTIMPs.

Related and unexpected events will require expedited reporting to the MHRA as SUSARs.

- Fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days after the research location is first aware of the reaction. Any additional relevant information must be sent within 8 days of the initial report.
- Non-fatal or non-life-threatening SUSARs must be reported as soon as possible but no later than 15 days after the research location becomes aware of the reaction.

The RGO, or designee will report the SUSAR to the MHRA through 'Individual Case Safety Report' (ICSR) submissions.

Where there are non-UK research locations, the relevant and specific reporting process for that country/location will be followed as outlined in the Risk Assessment and trial protocol.

All other trials (including clinical investigations of medical devices):
The expectedness assessment will be based on the list of expected events detailed in the approved version of the protocol at the time of the event occurrence.

Expectedness assessments must be performed by the PI or other medically qualified and delegated individual(s).

Related and unexpected events will require expedited reporting to the REC following the process outlined in the section 'Safety reporting for non-CTIMP studies' on the HRA website.

5.0 Unblinding Process for SUSARs – CTIMPs

The trial-specific unblinding process must be detailed within the protocol and must clearly state who is responsible for unblinding a participant in the event of a potential SUSAR.

Where a potential SUSAR has occurred, the responsible individual (as per the protocol) must unblind the participant before any expedited reporting. This is in order to provide meaningful information that enables a full evaluation of the data in the context of the safety profile of the drug(s). Blinded SUSAR reports will not be accepted by the regulatory authorities.

Care must be taken to protect the blind and it is advised that notifications to the CI and PI(s) regarding SUSARs are limited to:

“The Sponsor has been notified of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) for [Trial Name]. We have fulfilled our onward reporting obligations for this event if any was needed.”

Under no circumstances should notifications confirm the result of the unblinding OR whether or not a SUSAR has been submitted; to include either detail will unblind the recipient.

6.0 SUSAR reporting for Non CTIMPs

The non-CTIMP safety report form, available from HRA website, must be completed and emailed to the main REC alongside a copy of the RGO SAE Report Form B within 15 days of the research team becoming aware of the event. The RGO will email the report to the relevant REC, but the research team and CI are responsible for completing the non-CTIMP safety reporting form. Where relevant, as follow-up information becomes available, updated SAE reporting forms should be forwarded to the REC. The event will not be closed out by the RGO until confirmation that no further information is required by the REC is received.

7.0 Event Closure

Sponsor will issue a formal email confirming closure once all essential follow up information has been collected and the event is either fully resolved or has reached a stable state with no further expected changes.

If certain information cannot be obtained despite reasonable efforts, the sponsor may close the event with appropriate justification. In these cases, any new details that later emerge and could influence the event term, causality, expectedness, or outcome must be reported to the sponsor within the required timelines.

8.0 Pregnancy reporting – All trials

Pregnancy in a trial participant or their partner is not classified as a SAE, however a congenital anomaly or birth defect is. It is a regulatory requirement to follow-up all pregnancies occurring in CTIMPs to outcome.

A pregnancy notification form (Appendix 1, or alternative as agreed by the RGO), must be completed and sent to rgosponsor@le.ac.uk immediately and within 24 hours of awareness.

9.0 Urgent Safety Measures (USM) – All trials

Actions to protect participants from any immediate hazard to their health or safety are defined as ‘Urgent Safety Measures (USM)’ and can be implemented immediately. Notification and/or approvals are not required prior to their implementation but must be actioned immediately afterwards.

Refer to SOP S-1029 for full requirements regarding USMs, and SOP S-1018 for guidance on submitting amendments.

10.0 Development Safety Update Reports (DSURs) – CTIMPs

The CI (or delegate) must submit a DSUR annually for the duration of the trial, until the regulator has been notified of the end of the trial.

Refer to SOP S-1014 for full requirements.

11.0 Non-compliance

Where evidence of non-compliance is identified the Non-Compliance SOP S-1016 will be followed.

12.0 Development record

The table below summarises the revisions introduced in this version. Full historical change records are available within archived SOP versions.

Date	Version number	Description of changes
May 2026	8.1	• Typographical corrections