

**University of Leicester and University Hospitals of Leicester NHS
Trust joint Research Support Office Standard Operating
Procedures**

**University of Leicester Research Governance Office
SOP S-1009 UoL**

**Processing and reporting of serious adverse events, serious
adverse reactions and suspected unexpected serious adverse
reactions for all research sponsored by University of Leicester**

Office Base

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This SOP will be implemented in line with this document's effective date for all UoL Sponsored research still in set up. For active clinical research that is already in the recruitment phase (or further) at the time of implementation, this SOP must be implemented within 3 months of the effective date.

Please note the appendices associated with this SOP may be subject to interim changes. Please ensure that appendices are downloaded from the RGO webpages prior to use to ensure the latest version of the document is being used.

1.0 Introduction

This standard operating procedure (SOP) describes the requirements of the University of Leicester (UoL) for identifying, documenting and reporting all Adverse Events and Reactions when UoL are acting as research Sponsor.

The outcome is that the UoL fulfils the requirements as Sponsor to identify, document and report all categories of serious adverse events and reactions.

2.0 Purpose and scope

This SOP applies to all staff and external individuals involved in research activity sponsored by the UoL.

3.0 Definitions

3.1 Adverse Event (AE)

Is defined as “any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.”

3.2 Adverse Reaction (AR)

Is defined as “an untoward and unintended **response in a participant to an** investigational medicinal product, related to any dose administered.”

3.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Is defined as any adverse event or adverse reaction in a trial subject that:

- Results in death
- Is life threatening (the subject was at risk of death at the time of event)
- Requires hospitalisation or prolongation of an existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other serious important medical event - an event that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed above should be considered.

3.4 Suspected Expected Serious Adverse Reaction

Is defined as a serious adverse reaction, the nature and severity of which is consistent with the information about the medicinal product listed in the relevant reference documentation – Investigator Brochure (IB) or Summary of Product Characteristics (SmPC).

3.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Is defined as a serious adverse reaction, the nature and severity of which is not consistent with the applicable product information and / or approved Reference Safety Information in the investigator brochure (IB) or summary of product characteristics (SmPC).

Although these are the standard definitions, the reporting requirements of each study/trial may differ, dependent on the nature of the study/trial and the patient population.

Specific protocol reporting instructions should be followed.

4.0 Pregnancy reporting

Although pregnancy in a trial subject or their partner is not classified as a serious adverse event in itself, it is an important event, and there is a regulatory requirement to follow-up all pregnancies occurring in clinical trials of investigational medicinal products (CTIMPs) to outcome.

A pregnancy notification form (Appendix 1 – available from the RGO webpages, or alternative provided by the relevant drug company if agreed by Sponsor), must be completed and sent to rgosponsor@le.ac.uk within 24 hours of awareness.

5.0 SAE/SAR reporting procedure

5.1 AE/AR (Adverse events/adverse reactions)

There are no requirements to report these events to the Sponsor or regulatory agencies unless they are identified as critical to evaluations of the safety of the trial. AEs/ARs must be documented in the case report form (CRF) and patients' medical records (where appropriate) and observed to ensure that they do not escalate to a serious adverse event/reaction.

5.2 SAE/SAR – (Serious adverse event / adverse reactions)

All serious adverse events/reactions in studies sponsored by UoL must be reported to the Sponsor immediately and within 24 hours of the research team becoming aware of the event using the appropriate reporting form.

6.0 SAE/SAR reporting form

6.1 UoL sponsored CTIMP studies

The UoL Serious Adverse Event for CTIMP (Clinical Trials of Investigational Medicinal Products) Form A must be used*. This form and associated completion guidance document are available on the Research Governance webpages. This form and any documents provided to the Sponsor in support of the SAE **must not** contain any patient identifiable data. Note for non-CE marked medical devices see SOP 1043.

* For trials where a drug company requires additional information to that which is captured in the Sponsor SAE Reporting Form A, a trial-specific cover sheet can be used. A template cover sheet for trial-specific adaptation is available in Appendix 7. The cover sheet must be approved by the drug company **and** Sponsor prior to implementation. In exceptional cases, SAE reporting forms provided by the drug company may be used. This will be considered on a case-by-case basis and can only be implemented following approval by the Sponsor.

6.2 UoL sponsored non-CTIMP studies

For all non-CTIMP studies the UoL Serious Adverse Event Form B must be used. This form and associated completion guidance document are available from the Research Governance webpages. This form and any documents provided to the Sponsor in support of the SAE **must not** contain any participant identifiable data.

6.3 Review and sign-off for UoL sponsored studies

For UoL sponsored studies, the Principal Investigator (PI) or other medically qualified delegate are responsible for the review and sign-off of all SAEs at their site. After discussion with, and agreement by, the Sponsor, it may be possible for additional suitably qualified individuals to be delegated the responsibility for reviewing and signing off the SAE form. Anyone delegated

the duty of reviewing and signing-off SAEs must be recorded on the delegation of authority and signature log.

The CI should regularly review SAE listings.

6.4 UoL sponsored multi-centre studies

6.4.1 Multi-centre CTIMP

Where the study is a multi-centre CTIMP, all SAEs from all sites must be sent to the Sponsor as per UoL reporting requirements. Where sites are managed through a third party contractor e.g. a clinical trials unit, it may be appropriate to make alternative arrangements for reporting. These arrangements will be specifically detailed in the third party contract/agreement and it must be documented in the Risk Assessment. Where the delegation of SAE processing is granted at a later date, an amendment to the contract/agreement must be raised and this must be added to the Sponsor risk assessment. The Sponsor will ensure that the delegated party has appropriate experience and processes in place to undertake this delegated duty. Where alternative reporting arrangements have been agreed, the CI must regularly review SAE listings. The multi-centre CTIMP SAE listing table (Appendix 2) could be used where an alternative is not available. The line listing must be submitted to Sponsor as agreed and detailed in the agreement. All SAE line listings will be reviewed by the Director of R&I.

Sponsor maintain the right to either temporarily or permanently revoke the delegation of SAE processing responsibility at any point.

Details of SAEs occurring at collaborating sites must also be held centrally in the TMF.

6.4.2 Multi-centre non-CTIMP

Where the study is a non-CTIMP, all SAEs from each participating site must be sent to the Sponsor as per UoL reporting requirements. Details of SAEs occurring at collaborating sites must also be held centrally in the TMF. The multi-centre SAE listing table (Appendix 3) could be used where an alternative is not available.

7.0 Causality - (CTIMP trials only)

All causality assessments must be made by the PI (or other delegated medically qualified individual). The trial delegation log must reflect this. Where queries arise, the clinical judgement of the CI may be requested.

The definitions below must be used:

Causality Options	Definition
Unrelated	There is no evidence of a causal relationship to the investigational medicinal product.
*Related	There is evidence of a causal relationship to the investigational medicinal product

*may be defined as possibly, probably or definitely related

Events relating to placebo or reference drugs must also be reported.

8.0 Expectedness – (CTIMP studies only)

The approved reference safety information (RSI) found in the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) **MUST** be used to determine expectedness.

Expectedness assessment	Definition
Expected	<i>The event is an expected reaction based on the information contained in the Investigator Brochure (IB) and/or the Summary of Product Characteristics (SmPC).</i>
Unexpected	The event is Unexpected based on the information contained in the Investigator Brochure and/or the Summary of Product Characteristics.

Events relating to placebo or reference drugs must be reported.

Events leading to the death of a participant need to be reported to the Sponsor immediately and within 24 hours of the investigator becoming aware of the event, unless death is classified as an expected event which is exempt from reporting. Exemption to reporting events must be detailed in the approved protocol.

9.0 SUSARs (Suspected Unexpected Serious Adverse Reactions)

SUSARs are a subset of serious adverse reactions which are subject to strict mandatory expedited reporting timelines to the relevant Competent Authority (CA) and the main Research Ethics Committee(s) (REC). In the UK, the Competent Authority is the Medicines and Healthcare products Regulatory Agency (MHRA).

9.1 Reporting SUSARs in UoL Sponsored Trials

In a UoL sponsored trial, the responsibility of determining whether or not a reaction is a SUSAR is delegated to the PI. Where queries arise the clinical judgment of the CI may be requested. Where there are differences in opinion a conservative approach will be taken whereby both the opinion of the PI and Sponsor will be reported.

As for all SAEs, a SUSAR must be reported to the Sponsor immediately and within 24 hours of the research team becoming aware of it. The responsibility for expedited reporting to the CA and the main REC is that of the Sponsor.

9.1.1 SUSAR reporting for UK sites

In the UK, SUSAR reporting to the MHRA, is through ICSR submissions. Where UoL is the Sponsor, the responsibility of reporting a SUSAR using ICSR submissions is delegated by Sponsor to the PI, CI or appropriately qualified individual (e.g. Trial Manager). The PI may further delegate the responsibility to site staff, this must be recorded on the Delegation of Authority and Signature Log. Sponsor may undertake or facilitate the reporting process if required. Please refer to Appendix 10 for ICSR completion Guidelines.

When a SUSAR is identified, the Sponsor will immediately liaise with the study team to determine which of the following options will best facilitate reporting within the mandated timelines to the MHRA:

- a. Submission completed by Sponsor in conjunction with the PI or CI

- b. Submission completed by an appropriate member of the study team (e.g. Trial Manager) in conjunction with the PI or CI
- c. Submission completed by the PI or CI

Sponsor will ensure the appropriate accounts are created within ICSR submissions.

To avoid inactive accounts being frozen, Sponsor will only create individual investigator accounts in ICSR submissions as and when required (i.e., upon the identification of a SUSAR).

9.1.2 SUSAR reporting for non-UK sites

For CTIMP trials that have research sites outside of the UK, alternative and equivalent reporting systems may be in place for the relevant CA. During the Sponsor Review/Risk Assessment and/or Site Initiation Visit (SIV) for non-UK sites, the correct reporting process will be established and the trial protocol will provide guidance on the relevant process to be followed.

In all countries, fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days after the site 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 site becomes aware of the reaction.

All SUSARs identified in a trial where UoL is the Sponsor must be reported to the MHRA via ICSR submissions, irrespective of the country they occur in.

10.0 Blinded studies

In a blinded study, unblinding should be carried out prior to reporting a SUSAR to the MHRA (or equivalent for the Competent Authority). This is in order to provide meaningful information that can enable a full evaluation of the data in the context of the safety profile of the drug(s). Blinded SUSAR reports will not be accepted. Study-specific procedures for unblinding prior to reporting, will be discussed, and clearly documented, as part of the sponsor review process.

11.0 Urgent Safety Measures (USM)

The Sponsor and/or an investigator may take appropriate urgent safety measures to protect participants from any immediate hazard to their health and safety. The measures must be taken immediately. Approval is not required from the MHRA/CA, REC or HRA prior to implementation. However, where necessary, the measures must be discussed with the Sponsor, and the R&D/I department should be notified.

The REC and MHRA/CA must be notified immediately and in any event within 3 days that such measures have been taken and the reasons why they have been taken.

The process for submitting amendments as a result of Urgent Safety Measures is covered in SOP S-1018. In addition, Urgent Safety Measures are dealt with separately in the Urgent Safety Measures SOP S-1029.

12.0 Development Safety Update Reports (DSURs)

In addition to the expedited reporting required for SUSARs, Sponsors of CTIMP studies are required to submit a Development Safety Update Report (DSUR) to the MHRA/CA and REC

once a year throughout the term of the clinical trial or on request. Reports must be provided at yearly intervals from the date of the approval of the first trial of the Investigational Medicinal Product anywhere in the world (the Development International Birth Date (DIBD)).

Details about DSUR and the requirements may be found in SOP S-1014.

13.0 Research Ethics Committee reports for non-CTIMPs where the event is related and unexpected

SAEs occurring in research that do not involve an investigational medicinal product should be reported as per section 6 above.

Where in the opinion of the PI (or delegate) the event is related (that is, it resulted from administration of any of the research procedures), and unexpected (that is, the type of event is not listed in the protocol as an expected occurrence), the SAE report form for non-CTIMPs, available from HRA website should be completed and sent to the main REC within 15 days of the research team becoming aware of the event. A copy of the SAE form must also be submitted to the Research Governance Office.

14.0 Documentation

The following documentation must be available in the Trial Master File (TMF) and where relevant, the Investigator Site File (ISF)

- SAE, SAR and SUSAR reports and follow-up information
- AE / SAE Listing Table as evidence of submission and receipt of SAEs to the Sponsor within the required timelines
- Evidence of timely SUSAR submission to the MHRA/CA and main REC
- DSURs and evidence of their timely submission to the Sponsor, and subsequent forwarding from the Sponsor to the main REC and the MHRA where appropriate.

The investigator must ensure that all information relating to reportable events is recorded accurately in the study Case Report Form and medical records.

15.0 SAE review process

Sponsor acknowledgement of SAEs will be issued within 7 days of receipt. This acknowledgement must be filed in the TMF / ISF.

Each report will be registered on the recognised sponsor SAE database and reviewed. This review may lead to queries being issued to request signed documentation, clarify information or complete the outcome of the event. All queries will be sent via email and must be responded to within the timeframe stated within the response email. Please refer to Appendix 6 for a flowchart depiction of the review process.

All SAE/SUSARS reported to the Sponsor will be reviewed by the Director of R&I.

16.0 Non-compliance


Where evidence of non-compliance is identified the Non-Compliance SOP S-1016 UoL will be followed. Corrective actions will be expected in accordance with MAJOR findings.

17.0 Responsibilities

Responsibility	Undertaken by	Activity
CI/PI/Delegated individual	CI/PI/Delegated individual	Report all serious adverse events to the Sponsor (except those identified as exempt)
CI/PI/Delegated	CI/PI/Delegated individual	Follow up the initial report with a detailed written follow up/final report if not all information is available at the time of initial reporting
CI/Delegated Individual	CI/Delegated Individual	Completion of SAE Line Listing and review and sign off by CI/PI
CI/PI//Delegated individual	CI/PI//Delegated individual	Supply the Sponsor and the main REC with any additional information requested
CI/PI/Delegated individual	CI/PI/Delegated individual	Submit DSURs to Sponsor as per SOP S-1014 UoL
Sponsor	Sponsor	Ensures that all SUSARs are reported to the MHRA/CA and REC within mandatory timelines
Sponsor	Sponsor or delegate	Monitor all SAEs/SARs reported on a monthly basis to identify, and if necessary, act upon any emerging safety issues
Sponsor	Sponsor	Request and record receipt of, and forward DSURs to the main REC and MHRA/CA
Sponsor	Sponsor or delegate	The Sponsor will review SAE submissions and request further clarification/information as required to ensure SAE report completion. The CI/PI will be provided with Sponsor acknowledgement of receipt of the completed SAE.

18.0 Development and approval record for this document

This table is used to track the development and approval of the document.

Author	Job title	Reviewed by	Approved by	Date approved
Cat Taylor	Head of Research Governance	UoL Research Sponsorship Management and Operation Group (RSMOG)	Professor Nigel Brunskill 	09/03/2023

19.0 Review record

This table is used to track the changes made on revised/reviewed versions.

Date	Issue number	Reviewed by	Description of changes (If any)
Oct 2013	2.0	Wendy Gamble	Version 1 amended following review of Sponsor processes
May 2015	3.0	Wendy Gamble	Version 2 amended following review of Sponsor processes
Feb 2016	4.0	Diane Delahooke	Version 3 amended to include updated CTIMP form to include study medication and SAE amendment form replaced by SAE template email.
Nov 2016	5.0	Diane Delahooke	Addition of text in section 8 to make reference to the approved RSI. Reference to HRA added. Updating SAE form to reflect change in phone/fax numbers following move to Fielding Johnson Building. Also added extra appendix relating to multicentre reporting requirements.
August 2021	6.0	Cat Taylor	Minor text formatting Updated RGO office address Deletion of referral to RGO response email template Reordering of supporting appendices Addition of text in Section 6.1 regarding amending reporting templates to meet pharmaceutical company/ trial requirements. Addition of text in section 6.4.1 for when the SAE reporting process is delegated outside the Sponsor team Addition of text 6.4.1 Addition of text relating to reporting arrangements and agreements. Revision of text in section 6.4.1 regarding the review of SAEs by the Director of Research & Innovation. Revision of text in section 6.4.2 to supporting reporting requirements for multi-centre non CTIMP studies. Addition of new appendix – Appendix 4 eSUSAR completion guidelines in section 9. Revision of text in section 15 regarding the review of SAEs by the Director of Research & Innovation.
January 2023	7.0	Cat Taylor	Formatting to improve accessibility of SOP and appendices Significant updates to wording in line with legislation Updated reference to Research Governance Office webpages. Amendment to section 6.4.1 to provide clarification around the SAE delegation process Updates to SAE reporting forms Updates to SUSAR reporting via ICSR submissions