UNIVERSITY OF LEICESTER
&
UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST

JOINT RESEARCH SUPPORT OFFICE

STANDARD OPERATING PROCEDURES

University of Leicester (UoL) Research Governance Office
SOP S-1009 UoL

Version 6.0, September 2021

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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Effective Date: October 2021

1. Introduction

This standard operating procedure (SOP) describes the requirements of University of Leicester (UoL) for identifying, documenting and reporting all serious adverse events, serious adverse reactions and suspected unexpected serious adverse 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. Scope

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

3. 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 serious reaction

Is defined as an adverse reaction that in its nature is serious and 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 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. Pregnancy reporting

Although pregnancy in a trial subject or their partner is not classified as a serious adverse event in itself, it is however 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) must be completed and sent to the Research Governance Office. This is available on the College of Medicine, Biological Sciences and Psychology website (College Website), Research Governance pages.

5. 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. SAE/SAR reporting form

6.1 UoL sponsored CTIMP studies

The UoL serious adverse event for CTIMP Form A must be used*. This form and associated completion guidance document is available on the College Website, Research Governance pages. This form and any documents provided to the Sponsor in support of the SAE **must not** contain any patient identifiable data.

*The reporting template may be adapted to include additional fields to support pharmaceutical/trial reporting requirements. Permission must be sought from the Sponsor prior to changes being made. This will be considered on a case by case basis.

6.2 UoL sponsored studies NOT involving investigational medicinal products

For UoL sponsored studies NOT involving investigational medicinal products the UoL Serious Adverse Event Form B must be used. This form and associated completion guidance document is available on the College Website Research Governance pages. This form and any documents provided to the Sponsor in support of the SAE **must not** contain any patient identifiable data

6.3 Sign off and review for UoL sponsored studies

For UoL sponsored studies, the Chief Investigator (CI) or Principal Investigator (PI) is responsible for the review and sign off of all serious adverse events at their site. After discussion with, and agreement by, the Sponsor, it may be possible for additional medically qualified individuals to be delegated the responsibility for reviewing and signing off the SAE form.

This must be recorded on the delegation of authority and signature log.

The CI should regularly review SAE listings with the PI and Sponsor (where agreed).

6.4 UoL sponsored multi-centre studies

6.4.1 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 agreement or agreed by email by the Sponsor (evidence must be retained of this delegated responsibility and it must be documented in the Risk Assessment (where applicable)). Where alternative reporting

arrangements have been agreed the CI should regularly review SAE listings with the PI and Sponsor (where agreed).
The multi-centre CTIMP SAE listing table (Appendix 2) could be used where an alternative is not available. The line listing must be submitted as agreed and detailed in the agreement. All SAE line listings will be reviewed by the Director of R&I.

*Where the SAE review process is delegated to an individual outside of the Sponsor team, the following process will be adopted.
1. Sponsor to initiate the review process to provide overview of the types of queries raised and responses to be sent.
2. Delegated individual/ team review reports and respond to teams with the oversight of the Sponsor. Where required the Sponsor will provide additional guidance and training.
3. Sponsor to maintain oversight of the SAEs and liaise with delegated teams if required. Upon the adoption of point 3, the delegated individual/team will be issued a file note confirming the responsibility of SAE review.

6.4.2 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. The multi-centre SAE listing table (Appendix 3) could be used where an alternative is not available.

7. Causality (CTIMP studies only)

Any causality assessments must be made by the CI/ PI or the Sponsor agreed delegated medically qualified individual. The trial delegation log must reflect this.

The definitions below can be used:

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

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

8. Expectedness – (CTIMP studies only)

The <u>approved</u> reference safety information (RSI) i.e. investigator brochure or summary of product characteristics MUST be used to determine expectedness.

Expected	The event is **expected** based on the information contained in the Investigator Brochure and/or the Summary of Product Characteristics.

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 trial participant need to be reported to the Sponsor immediately once the investigator becomes aware of the event, unless death is classified as an expected event and is therefore exempt from reporting. Exemption to reporting events must be detailed in the approved protocol.

9. SAR/SUSARs (serious adverse reaction/suspected unexpected serious adverse reactions)

SAR/SUSARs are a subset of serious adverse reactions which are subject to strict mandatory expedited reporting timelines to the Medicines and Healthcare products Regulatory Agency (MHRA) and the main Research Ethics Committee (REC).

In a UoL sponsored study, the responsibility to evaluate whether or not a reaction is a SUSAR is delegated to the PI or CI.

As for all SAEs, a SUSAR must be reported to the Sponsor with immediate effect and within 24 hours of the research team becoming aware of it. The responsibility to report to the MHRA through the eSUSAR system and the main REC is that of the Sponsor, but this is delegated to the CI for completion. Please refer to Appendix 4 for eSUSAR completion guidelines.

The initial report must be submitted as soon as possible and, within 7 calendar days for a death or life threatening SUSAR (and submit any follow up information within an additional 8 calendar days) or within 15 calendar days for other SUSARs.

9.1 UoL sponsored CTIMP studies

Where UoL is the Sponsor, the responsibility to report the SUSAR using eSUSAR to the MHRA is delegated to the CI or PI or appropriately qualified individual approved by the Sponsor. This delegated task will be discussed and confirmed with the individual during the Sponsor review process.

In addition, the CI/PI is responsible for the completion of the CIOMS form which must be sent to the Sponsor, whose responsibility it will be to submit to the REC and MHRA.

10. Blinded studies

In a blinded study, unblinding must be carried out prior to reporting a SUSAR to the MHRA. Study specific procedures for unblinding prior to reporting, will be discussed, and clearly documented, as part of the sponsor review process.

11. Urgent safety measures

The Sponsor and investigator may take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. The measures must be taken immediately; Sponsor, MHRA, REC, HRA and R&D approval is not required before implementation, however all parties must be informed in writing, in the form of a substantial amendment within three days. The process for submitting amendments as a result of Urgent Safety Measures is covered in the Amendment SOP S-1018 UoL. In addition Urgent Safety Measures are dealt with separately in the Urgent Safety Measures SOP S-1029.

12. 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 and main 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).

Ideally the DSUR will be produced by the authorisation holder for that first trial but it is recognised that this may not always be feasible and the MHRA will accept DSURs on a per sponsor per study basis if it is not possible to collaborate with other interested parties.

The DSUR is required in addition to the Annual Progress Report required by the main REC.

The aim of the DSUR is to assure regulators that Sponsors are adequately evaluating and monitoring the safety profile of an IMP. It provides an overview of all ongoing trials and other studies, including those that have been interrupted, that the Sponsor is conducting / has completed during the review period. The DSUR should describe concisely all new safety information relevant for one or several clinical trial(s) and assess the safety of subjects included in the studies. A DSUR is still required even if there is no new safety data to report.

Full details of what to include in a DSUR can be found in a separate SOP (SOP S-1014 UoL) available on the College Website, Research Governance Pages..

For UoL sponsored studies the responsibility for producing DSURs is delegated to the CI/PI. Reports must be sent by the CI/PI to the Sponsor, who will then forward them to the main REC and the MHRA.

13. Ethics committee reports for clinical trials of non-investigational medicinal products 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 CI or PI the event was 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 CI or PI becoming aware of the event. A copy of the SAE form must also be submitted to the Research Governance Office.

14. Documentation

The following documentation must be available in the Trial Master File (TMF) / Investigator Site File (ISF)

- SAE, SAR and SUSAR reports and follow-up information
- SUSAR reporting guidelines and SAE reporting guidelines
- AE / SAE Listing Table (Appendix 5)
- Evidence of submission and receipt of SAEs to the Sponsor within the required timeframe.
- Evidence of timely SUSAR submission to the MHRA 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.

The investigator must ensure that all SAE information is recorded accurately in the study Case Report Form.

15. SAE review process

Sponsor acknowledgement will be issued to the investigator within 7 days of receipt of a fully completed form.

Each SAE 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. 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. Responsibilities

	Responsibility	Undertaken by	Activity
1	CI/PI/Delegated individual	CI/PI/Delegated individual	Report all serious adverse events to the Sponsor (except those identified as exempt)
2	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
3	CI/Delegated Individual	CI/Delegated Individual	Completion of SAE Line Listing and review and sign off by CI/PI
4	CI/PI//Delegated individual	CI/PI//Delegated individual	Supply the Sponsor and the main REC with any additional information requested
5	CI/PI/Delegated individual	CI/PI/Delegated individual	Submit DSURs to Sponsor as per SOP S-1014 UoL
6	Sponsor	Sponsor	Ensures that all SUSARs are reported to the MHRA and REC within mandatory timelines
7	Sponsor	Sponsor or delegate	Monitor all SAEs/SARs reported on a monthly basis to identify and if necessary act upon any emerging safety issues
8	Sponsor	Sponsor	Request and record receipt of, and forward DSURs to the main REC and MHRA
9	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.

This table is used to track the development and approval of the document and any changes made on revised / reviewed versions

18 Development and approval Record for this document

Author / Lead Officer:	Cat Taylor
Job Title:	Head of Research Assurance
Reviewed by:	UoL Research Management and Operations Group (RSMOG)
Approved by:	Professor Nigel Brunskill 
Date Approved	13/10/2021

19 Review Record

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
Oct 2013	2	Wendy Gamble	Version 1 amended following review of Sponsor processes
May 2015	3	Wendy Gamble	Version 2 amended following review of Sponsor processes
Feb 2016	4	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	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	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.

20 Distribution Record

Date	Name	Department	Received