1. Introduction

This Standard Operating Procedure (SOP) describes the process required by the University Hospitals of Leicester NHS Trust (UHL) for identifying, documenting and reporting all Adverse Events and Reactions when UHL are acting as research Sponsor.

The outcome is that the UHL fulfils the requirements as Sponsor to appropriately 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 UHL.

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 (SPC).

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 (SPC).

Although these are the standard definitions, the reporting requirements of each study may differ, dependent on the nature of the study and the patient population. Specific protocol reporting instructions should be followed.

4. Pregnancy Reporting

Although pregnancy in a study 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 Office. This is available on the R&I pages of the UHL public website.

5. 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 study. 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 UHL 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 UHL Sponsored CTIMP studies

The UHL Serious Adverse Event for CTIMP (Clinical Trials of Investigational Medicinal Products) **Form A** must be used. This form and associated completion guidance document are both available on the R&I Website. This form and any documents provided to the Sponsor in support of the SAE MUST not contain any participant identifiable data. * NOTE for Non-CE marked medical device studies see SOP S-1040

6.2 UHL Sponsored Studies NOT involving Investigational Medicinal Products

For UHL sponsored studies NOT involving Investigational Medicinal Products the UHL (for example qualitative or non IMP interventions) Serious Adverse Event **Form B** must be used. This form and associated completion guidance document are both available on the R&I website. This form and any documents provided to the Sponsor, in support of the SAE, MUST not contain any participant identifiable data. * NOTE for CE marked medical device studies see SOP S-1041

6.3 Sign Off and of Review for UHL Sponsored Studies

For UHL sponsored studies, the 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 log.

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

6.4 Multi-Centre

6.4.1 Where the study is a CTIMP all SAEs from all sites must be sent to the Sponsor as per UHL 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. Where alternative reporting arrangements have been agreed, details of all SAEs occurring at all sites, must be completed/reviewed by the CI. The multi-centre CTIMP SAE Listing table (Appendix 6) could be used where an alternative is not available. The line listing must be submitted as detailed in the agreement. All SAE listings will be reviewed by the Director of R&I at the monthly R&I management meeting

6.4.2 Where the study is a non CTIMP, the SAEs for the lead site must be submitted to the Sponsor unless managed through a third party. Details of SAEs occurring at collaborating sites must be reviewed by the C I. The multi centre SAE listings table (Appendix 2) could be used where an alternative is not available. These must be submitted to the Sponsor as detailed within the agreement. 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.
Where alternative reporting arrangements have been agreed, details of all SAEs occurring at all sites, must be completed/reviewed by the CI. The multi-centre CTIMP SAE Listing table (Appendix 6) could be used where an alternative is not available. The line listing must be submitted as detailed in the agreement. All SAE listings will be reviewed by the Director of R&I at the monthly R&I management meeting

7. Causality – IMP Studies ONLY

Any causality assessments must be made by the PI or the Sponsor agreed delegated medically qualified individual. The study 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 – IMP Studies ONLY

The approved 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 study 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 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 mandatory expedited reporting timelines to the Medicines and Healthcare products Regulatory Agency (MHRA) and the main Research Ethics Committee (REC).

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

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. An 'eSUSAR' reporting guidance document is available at Appendix 7. The Sponsor process for ensuring SUSARs are appropriately reported is available at Appendix 8. A template email notifying all sites (where multi-centre) is available at Appendix 9.

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. SUSARs for UHL Sponsored Studies are additionally tracked through EDGE.

9.1 UHL Sponsored CTIMP Studies

Where UHL 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 & MHRA.

9.2 Blinded Studies

In a blinded study, unblinding must be carried out prior to reporting a SUSAR to the MHRA (appendix 10). Study specific procedures for unblinding prior to reporting, will be discussed and clearly documented as part of the sponsor review process.

10. 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 & R&I 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 SOP S-1018 UHL SOP S-1026 UHL.

11. 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 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). Details about DSUR and the requirements may be found in SOP S-1004 UHL which is available on the R&I public website.

12. Ethics Committee Reports for Clinical Trials of Non-Investigational Medicinal Products where the event is related and unexpected.

SAEs occur in research that does not involve an Investigational Medicinal Product. These SAEs should be reported as per 6 above.

Where in the opinion of the 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 the Health Research Authority (HRA) website should be completed and sent to the main REC within 15 days of the PI becoming aware of the event. A copy of the SAE form must also be submitted to the Research Office.

13. 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
- AE / AR / SAE Logs
- 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.

14. SAE Review Process

Sponsor acknowledgement will be issued to the Investigator within 7 days of receipt of a fully completed form. This acknowledgement must be filed in the TMF / ISF.
Each SAE will be registered on the recognised Sponsor database and reviewed. The whole SAE process will be managed through the EDGE system. Please see Flow Chart (Appendix 4). The review may lead to queries being issued to request signed documentation, clarify information or complete outcome of the event. All queries will be sent via email and must be responded to within the stated timeframe as per the SAE Template Email (Appendix 5).

All SAE/SUSARS reported to the Sponsor will be reviewed and where appropriate formally signed off at the R&I Management Meeting by the Director of R&I.

15. Non-Compliance

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

16. Responsibilities

	Responsibility	Undertaken by	Activity
1	PI/Delegated individual	PI/Delegated individual	Report all serious adverse events to the Sponsor (except those identified as exempt)
2	PI/Delegated individual	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//PI/Delegated Individual	CI/PI/Delegated Individual	Completion of SAE line listing and review and sign off by Chief Investigator
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-1004 UHL
6	Sponsor	Sponsor	Ensures that all SUSARs are reported to the MHRA and REC within mandatory timelines
7	Sponsor	Sponsor	Monitor all SAEs/SAR line listings reported on a monthly basis to identify and if necessary act upon any emerging safety issues
8	Sponsor	Monitor	The Monitor 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.

17. Supporting Documents and Key References

SOP S-1009 Appendices 6, 7, 8, 9, 10
SOP S-1009 UHL SAE Form A Completion Guidance Document CTIMP
SOP S-1009 UHL SAE Form B Completion Guidance Document Non-CTIMP
SOP S-1009 UHL SAE Reporting Form A CTIMP
SOP S-1009 UHL SAE Reporting Form B Non-CTIMP
SOP S-1018
SOP S-1026
SOP S-1004
SOP S-1016

18. Key Words

Research, Innovation, Volunteers, Participants, SAE, SAR, SUSAR, ATIMPS, CTIMPS, Trial, Adverse Events, Serious Adverse Events

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

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Feb 2017	8	Carolyn Maloney	Version 8 amended Logo
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