1. Introduction

This Standard Operating Procedure (SOP) describes the process for identifying, documenting and reporting all Adverse Events and Reactions where the University Hospitals of Leicester are acting as a HOST organisation or a research SITE and where the UHL is **NOT** the Sponsor.

This SOP must not be used where UHL is acting as the research Sponsor. In this case SOP S-1009 UHL must be used.

The outcome is that the UHL fulfills the requirements as a HOST Organisation or research SITE 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 HOSTED by UHL or where UHL is a research SITE.

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.”

Note* An adverse event can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom, or disease in any subject in a clinical trial(including those in an untreated control group, whether or not considered related to the interventional medicinal product

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.” All adverse reactions are adverse events.

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 of serious adverse events, the reporting requirements of each study may differ, dependent on the nature of the study and the patient population. Specific protocol and / or Sponsor reporting instructions should be followed.

4. Pregnancy Reporting in Clinical Trials of Investigational Medicinal Products

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 must be completed and sent to the Research Office within 24 hours of the study team becoming aware of the pregnancy. The pregnancy must be followed to conclusion. If the Sponsor of the research is unable to provide a template for this purpose, then the UHL Pregnancy Notification Form (Appendix 1) may be used. This is available on the R&I pages of the UHL public website. Once a relevant form has been completed please send to the Research & Innovation Office by email to RIAdmin@uhl-tr.nhs.uk

5. Reporting Procedure

The Principal Investigator must ensuring that study personnel are suitably trained for the purposes of AE recording, assessment and reporting.

5.1 AE/AR (Adverse Events/Adverse Reactions)

AEs/ARs must be documented in accordance with the Sponsor requirements. They should always be documented in the Case Report Form (CRF) and patients' medical records and observed to ensure that they do not escalate to a serious adverse event.

All serious adverse events in studies HOSTED by UHL or where UHL is the research SITE must be reported to the Sponsor in accordance with the Sponsor SOP.

5.2 SAE/SAR Reporting

5.2.1 HOSTED CTIMP studies where UHL is a research SITE

It is expected that all SAEs / SARs be reported to the Sponsor in accordance with the Sponsor SOP.

Reports should include as much information as is available to the investigator at the time, and make clear the investigator's assessment of intensity, causality and expectedness. The principal Investigator/ delegate are responsible for the review, assessment of causality and expectedness and sign off of all SAES.

Assessment Criteria (unless otherwise specified in the Research Protocol)

5.2.1.1 Intensity

The assessment of an event's intensity will be based upon the investigator's clinical judgement using the following definitions:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

- Severe: An event that prevents normal everyday activities.

Note: The term severity is often used to describe the intensity (severity) of a specific event. This is not the same as 'seriousness', which is based on patient/event outcome

5.2.2.2 Causality

The relationship between an adverse event and the study interventions, IMP or procedures, **must** be assessed by the Principal Investigator or delegate and categorised as below.

The assessment will be based upon the investigators/delegates clinical judgement to determine the relationship, considering alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. The Investigator/delegate should consult the protocol, Investigator Brochure, SmPC and any other product information which has been approved by the MHRA before making a final judgement that the event is one of the following:

- **Not related:** Temporal relationship of the onset of the event, relative to administration of the product or procedure, is not reasonable or another cause can by itself explain the occurrence of the event.

- **Unlikely to be related:** Temporal relationship of the onset of the event, relative to administration of the product or procedure, is likely to have another cause which can by itself explain the occurrence of the event.

- **Possibly related:** Temporal relationship of the onset of the event, relative to administration of the product or procedure, is reasonable but the event could have been due to another, equally likely cause.

- **Probably related:** Temporal relationship of the onset of the event, relative to administration of the product or procedure, is reasonable and the event is more likely explained by the product/procedure than any other cause.

- **Definitely related:** Temporal relationship of the onset of the event, relative to administration of the product or procedure, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive. Note: Where an event is assessed as possibly probably, or definitely related, the event is an adverse reaction.

5.2.2.3 Expectedness

The expectedness of an adverse event, **must** be assessed by the Principal Investigator or delegate.

Expectedness is categorised as below (by itself explain the occurrence of the event):

- Shall be determined according to the reference documents as defined in the study protocol (e.g. investigator brochure or marketing information). Adverse events should be considered unexpected if they add significant information on the specificity or severity of an event, which is expected.

- **Expected:** Event is previously identified and described in the protocol and/or reference documents e.g. Investigator Brochure, summary of product characteristics (SPC) for CTIMP studies.

- **Unexpected:** Event is not previously described in the protocol or reference documents.

If the investigator suspects the event to be a SUSAR (Suspected, Unexpected Serious Adverse Event) this should be clearly identified on the report form.

SUSARs must be reported to the Sponsor and R&I office within 24hrs of the study team being made aware of the event.

5.2.2 SAR Reporting for Hosted Studies

UHL Research office requires an annual line listing of all adverse events. A template is available for completion if the Sponsor is unable to produce a suitable listing (Appendix 2).

Annual line listings should be completed and sent to the R&I Office on or within 28 days of the anniversary of HRA/MHRA Approval. UHL R&I will remind the study teams when this is due. Reminders will commence with effect from 1st March 2015. The line listing should have a date later than 1st August 2014 onwards initially, then annually thereafter. The line listing appended to an Annual Report can be sent provided that the information is UHL Specific. There is no requirement for an additional report to be generated.

In cases where there have been no SAEs reported within the 12 month period, a NULL report for the study must be submitted.

It is the responsibility of the Principal Investigator (PI) at UHL to ensure that **R&I Office** is notified if there are unacceptable patterns of SAEs emerging from a protocol which have the potential to affect the care or safety of the patient.

If a Sponsor takes the decision to prematurely stop or suspend a study, the PI must notify the R&I Office within 24 hours of notification.

5.3 HOSTED Studies not involving Investigational Medicinal Products where UHL is the research SITE

It is expected that all SAEs / SARs be reported to the Sponsor in accordance with the Sponsor SOP. With effect from 1st August 2014 there is no requirement to report SAEs to the Research Office within 24 hours of the research team becoming aware of the event.

Reports should include as much information as is available to the investigator at the time, and make clear the investigator's assessment of intensity, causality and expectedness. The principal Investigator/ delegate are responsible for the review, assessment of causality and expectedness and sign off of all SAES.

UHL Research office requires an annual line listing of all events. A template is available for completion if the Sponsor is unable to produce a suitable listing. (Appendix 3)

Annual line listings should be completed and sent to the R&I Office on or within 28 days of the anniversary of HRA/MHRA approval. UHL R&I will remind the study

teams when this is due. Reminders will commence with effect from 1st March 2015. The line listing should have a date later than 1st August 2014 onwards initially, then annually thereafter. The line listing appended to an Annual Report can be sent provided that the information is UHL Specific. There is no requirement for an additional report to be generated.

In cases where there have been no SAEs reported within the 12 month period, a NULL report for the study must be submitted.

It is the responsibility of the Principal Investigator at UHL to ensure that R&I Office is notified if there are unacceptable patterns of SAEs emerging from a protocol which have the potential to affect the care or safety of the patient.

6. R&I Office Process

As part of the Capacity and Capability review a Study Support Officer will add a reminder for 'SAE Line Listing due' to the Global Calendar in EDGE. The due date is the anniversary of HRA or MHRA (CTA)(whichever is the soonest) approval. The Global Calendar Entry will be categorised as 'Audit'. An additional Global Calendar date will be added 31 days prior to the due date as 'SAE Line Listing Due Notification'. NB as this process has been introduced in 2020 all studies active and reporting SAEs on 1st January 2021 onwards will have the calendar entries added along with the relevant workflow. The delay is to allow time to add the workflows and to accommodate additional pressure on resource due to COVID19.

When the notification appears on the calendar reminders listing a standard email (Appendix 4) will be sent to the Research Team, copied to the PI requesting that the line listing for UHL be returned by the due date. If the Line Listing is not received a reminder email will be sent on the due date (Appendix 5) with a further follow-up sent 14 days later (Appendix 6).

If a Line listing is not received on the third request the Non-compliance SOP C-2013 UHL will be implemented at a Major finding.

Once received an acknowledgement email will be sent (Appendix 8) and completion of EDGE Workflow 'RICORP SAE Line Listing (Host) will be started. The Line Listing will be added to the files in Red Level of EDGE for the relevant study.

The Line Listing will be checked for completeness by the UHL Clinical Trials Monitor. If complete, the Line Listing will be added to the next monthly R&I Governance Meeting Agenda, and in parallel sent to the Directors of R&I for a medical oversight review. If not complete a request to amend the document will be made with a deadline 7 days later (appendix 7). It is likely that there will be multiple reports received during the month and a single collated report will be produced. Any queries or points for clarification will be directed to the PI and Research Team as appropriate.

Where there are no further queries or points for clarification the reports will be filed within the meeting papers and the EDGE workflow updated/ completed.

7. Delegation of Authority Log

The Principal Investigator (PI) is responsible for the review and sign off of all serious adverse events. 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.

UHL requires that adequate processes are in place to ensure cover for review of SAE/SUSARs by a delegated medic, where either planned or unplanned leave is taken by the Principal Investigator. This must be in place before study commencement and updated as applicable during the timespan of the study. This must be recorded on the Delegation of Authority Log which must be stored in the Investigator Site File (ISF).

8. SAR/SUSARs (Serous Adverse Reaction / Suspected Unexpected Serious Adverse Reactions)

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

In a study hosted by UHL or where UHL is a research SITE, it is expected that the Sponsors SOP be followed.

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. In all cases of SUSARs at UHL, notification must be made to the R&I Office within 24 hours of becoming aware of the SUSAR, and kept informed of any action required, taken or proposed by the Investigator/s or the Sponsor.

9. Urgent Safety Measures (USM)

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 approvals are not required before implementation. However, they must be informed in writing, in the form of a substantial amendment within three days. It is expected that the R&I Office be notified of any USMs, the immediate action required, undertaken and any amendments following the USM. Information regarding the SUSAR will be uploaded to EDGE and RICORPS SUSAR Process workflow completed.

10. 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	Provide an annual line listing of SAEs to the R&I Office
3	PI/Delegated individual	PI/Delegated individual	Identify subjects by trial study number and initials, this information should be recorded on all reports. No personal identifiable data should be recorded on the SAE form or supporting documentation

11. Legal Liability Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or Procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional it is fully appropriate and justifiable – such a decision to be fully recorded in the patient's notes and in the research site file.

12. Supporting Documents and Key References

SOP C-2002 Appendices 1, 2, 3, 4, 5, 6, 7, 8 & 9
SOP S-1009
SOP C-2013

13. Key Words

Research, Innovation, SUSAR, SAE, Studies, Trials, Adverse, Reaction, EDGE, MHRA, SAR, AE, AR

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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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REVIEW RECORD

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
Oct 2015	2	Carolyn Maloney	Changes to wording & Logo changes
June 2016	3	CM, LW, AG, SA LB	Consistency check. Addition of legal liability statement. Reformatting. Version of appendices to correlate with SOP
February	4	Carolyn Maloney	Update to logo.
February 2019	5	CM, LW	Review, wording clarification.
February 2021	6	LW, JJ,AM	Review, consistency checks, reformatting to trust guideline template. Clarification of delegation requirements and SAE/SUSAR reporting and R&I office processes, Reformatting to new template
Sept 2021	8	LW JJ	Consistency

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