



**University of Leicester Research Governance Office
Standard Operating Procedures**

SOP S-1043 UoL

**Processing and Reporting Serious Adverse Events and Serious
Adverse Device Effects for Medical Device Studies Sponsored by the
University of Leicester**

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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 and Scope

This Standard Operating Procedure (SOP) applies to all staff involved in research activity sponsored by the University of Leicester (UoL) involving non-CE/UKCA marked devices or CE/UKCAE marked devices that are being used outside their intended use(s) covered by the CE marking that require MHRA approval. It describes the process required by the UoL for identifying, documenting and reporting all adverse events (AEs) in medical device studies.

In order to comply with the appropriate legislation, all researchers must be aware of the definitions and procedures in relation to AEs for medical device studies. This legislation includes:

- Medical Device Regulations 2002
- Medical Device Directives 90/385/EEC and 93/42/EEC, ISO 14155:2011 (Clinical investigations of medical devices for human subjects – Good Clinical Practice)

2.0 Definitions

2.1 CE Mark

CE marking is an administrative **marking** that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area

2.2 UKCA Mark

The UKCA (**UK Conformity Assessed**) marking is a new UK product marking that is used for goods being placed on the market in Great Britain (England, Wales and Scotland) from the 1st January 2021

2.3 Medical Device

A medical device is defined as any instrument, apparatus, appliance, material or other article, whether used alone or in combination with any software necessary for its proper application which is:

a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury
- Investigation, replacement, modification, or support of the anatomy or of a physiological process
- Supporting or sustaining life
- Control of contraception
- Disinfection of medical devices

b) Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

This definition of medical device is as per ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice and **does not apply to *in vitro* diagnostic medical devices** (which is covered by ISO 13485:2003).

2.4 Investigational Medical Device

An Investigational Medical Device is a medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

2.5 Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

2.6 Device Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan (CIP).

2.7 Clinical Investigation Plan (CIP)

A document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record keeping of the clinical investigation.

2.8 Investigator's Brochure (IB)

A compilation of the current clinical and non-clinical information on the investigational medicinal device relevant to the clinical investigation.

2.9 Adverse Event (AE)

An adverse event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device/intervention.

2.10 Adverse Device Effect (ADE)

An adverse device effect (ADE) is an adverse event that is deemed to be **related** to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

An ADE includes any event that is a result of use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

2.11 Serious Adverse Event (SAE)

In medical device studies a Serious Adverse Event (SAE) is defined by ISO14155:2011 guidelines for medical device studies as an untoward occurrence in a trial subject that:

- led to a death
- led to serious deterioration in the health of the participant, that either resulted in:
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function
 - in patient hospitalisation or prolonged in-patient hospitalisation

- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note 1: This also includes device deficiencies that might have led to a SAE if:

- suitable action have not been taken
- intervention had not been made
- if circumstances had been less fortunate

Note 2: A planned hospitalisation for a pre-existing condition, or procedure required by the Clinical Investigation Plan (CIP) without a serious deterioration in health is not considered to be a serious adverse event.

2.12 Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

These can be divided into two categories;

2.12.1 Anticipated Serious Adverse Device effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has **been previously identified** in the current version of the Risk Assessment or the Investigator's Brochure.

2.12.2 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Risk Assessment and/or Investigator's Brochure.

3.0 Identification and Recording of Adverse Events

The Principal Investigator (PI) at site or designee, is responsible for the identification of any AE as defined in the protocol/CIP. AEs/ADEs defined as non-serious in nature must be recorded in the medical records and the Adverse Event/Device Effect record (Appendix 2) and retained with the case report form (CRF).

All AEs/ADEs must be observed to ensure that they do not escalate to an SAE/SADE. There are no requirements to report AEs/ADEs to the Sponsor or Regulatory Agencies unless the AE/ADE meets the criteria of a SAE/SADE where the procedure described in section 4 must be followed.

4.0 Reporting of SAEs and SADEs

4.1 Reporting to Sponsor

All SAEs/SADEs (whether ASADEs or USADEs) 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 unless they are listed in the protocol/CIP as expected events.

UoL Serious Adverse Event/Device Effect Report Form C for medical device studies (Appendix 3) must be used. This form and associated completion guidance

document are both available on the RGO Website. This form and any documents provided to the Sponsor in support of the SAE/SADE must be pseudonymised and must not contain any patient identifiable data.

For UoL Sponsored studies, the Chief Investigator (CI) or Principal Investigator (PI) or the Sponsor delegated qualified individual is responsible for the review and sign-off of all serious adverse event/effects. In the event that the CI/PI is unable to sign the report immediately, the research team/site should not delay sending the report, however a CI/PI signed copy must be forwarded to the Sponsor as soon as possible (and within 7 days of the initial reporting).

The research team/site must provide any additional information actively following-up the subject until either:

- The SAE/SADE resolves, or
- The Sponsor and CI/PI agree that no further follow-up is required*

*This decision must be documented in the CRF

After discussion with, and in 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.

4.1.1 Multi-Centre studies

All SAEs and SADEs from participating sites must be sent to the Sponsor. 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. All SAEs/SADEs will be reviewed by the Director of R&I as part of a monthly line listing, and are discussed at the Research Sponsorship Monitoring & Oversight Group (RSMOG). Events resulting in fatality and those considered related to the device/intervention are expedited to the Director of R&I and/or the insurance team as relevant. Should a USADE be reported at any site, the Sponsor (or delegate) will inform all participating site PI's . Where required all medical devices at all sites will be quarantined until the MHRA investigation has been completed.

4.2 Reporting to MHRA

The following events are considered reportable to the MHRA in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of Directives 90/385/EC and 93/42/8EEC respectively:

- Any SAE
- Any device deficiency that might have led to a SAE if:
 - Suitable action had not been taken or
 - Intervention had not been made or
 - If circumstance had been less fortunate
- New findings/updates in relation to already reported events

For all reportable events where there is an imminent risk or death, serious injury or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: the sponsor or designee must report to the MHRA immediately, but no later than **2 calendar days** after they become aware of such an event or new information in relation to an already reported event.

Any other reportable events as outlined above or any new finding/update in relation to them must also be reported immediately, but no later than **7 calendar days** after the sponsor becomes aware of them.

The sponsor (or their delegate) must notify the MHRA via the MORE portal. For registration and guidance please refer to the [GOV.UK website](https://www.gov.uk).

4.3 Reporting to REC

The following SAEs/SADEs are considered reportable to the REC that gave the favourable ethical opinion:

- Those related to the administration of the medical device or any of the research procedures.
- USADEs- i.e. unanticipated events not listed in the Risk Assessment/Protocol as an anticipated occurrence.

Reports should be submitted within 15 days of the CI becoming aware of the event using the Non-CTIMP Safety Report Form to the REC published on the HRA website <http://www.hra.nhs.uk/>

The CI is also required to include a report of the safety of participants in the annual progress report to the REC.

Individual reports will be reviewed by the REC at a subcommittee or committee meeting. Any requests for further information should be provided as applicable and all correspondence should be copied to the Sponsor.

4.4 Reporting to NHS Trust

Where applicable, SAEs/SADEs which occur at site must be reported on the Trusts electronic incident reporting system (e.g. Datix). Reporting of incidents must be carried out in accordance with the local Trusts Incident and Accident reporting policy.

5.0 Assessment of Adverse Events

All assessments of AEs must be made by the CI/PI or the Sponsor agreed delegated medically qualified individual. The study Delegation of Authority and Signature Log must reflect this (Appendix 2 SOP S-1021).

Each AE must be assessed for seriousness, severity, causality and expectedness. Where there are two assessments of causality, for example, the CI/PI assessment do not concur, the causality made by the Investigator cannot be downgraded.

5.1 Assessment of Seriousness

The assessor should make an assessment of seriousness as defined in section 2.11 Serious Adverse Events.

5.2 Assessment of Severity

The relationship between the investigational medical device and the occurrence of each adverse event must be assessed utilising the device event categorisation flow chart (Appendix 1).

5.3 Assessment of Causality

Causality is an assessment of the relationship between the device and the event.

The assessor of any causality assessments will use clinical judgement to determine

the relationship. The assessor must consult the current version of the Risk Assessment and/or the Investigator's Brochure where available.

When making a causality assessment, the following definitions should be used:

Not related	There is no evidence of causal relationship to the Investigational Device.
Unlikely	The relationship with the use of the investigational medical device seems not relevant and/or the event can be reasonably explained by another cause.
Possible	The relationship with the use of the investigational medical device is weak but cannot be ruled out completely.
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot reasonably be explained by another cause.
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt.

5.4 Assessment of Expectedness

The assessor must consult the current version of the CIP and/or IB to determine whether an event is expected. Where applicable in blinded studies, unblinding must occur to assess treatment assignment.

If the event is classified as an anticipated effect this event does not require reporting to the Sponsor or Regulatory Agencies but must be recorded in the medical records and the adverse event record (Appendix 2). This document must be retained with the case report form.

Where an event could be related to the medical device and is unanticipated in relation to the CIP/IB, the Investigator must report this event immediately or within 24 hours to the Sponsor/manufacturer and to the regulatory agencies within the required timelines.

Where applicable in blinded studies, unblinding must occur to assess treatment assignment.

6.0 Quarantine of Devices

The device must not be returned to the manufacturer until the MHRA has been given the opportunity to carry out/complete an investigation, if required. In addition, the device **should not** be:

- Discarded
- Repaired
- Returned to the manufacturer
- Removed from the site/organisation premises without previous agreement from the Sponsor

All material evidence (i.e., devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification) **must** be:

- clearly identified and labelled
- stored securely

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions of switches, valves, dials, gauges and indicators, together with photographic evidence and eyewitness reports.

N.B: Consideration should be given to the practicality and implications of quarantining the device; for example if the device is an implantable device all further supplies of the device should be quarantined as a precaution until further advice is sought.

The Investigator and the Sponsor will undertake any requirements outlined in the MHRA investigation and follow-up as instructed.

7.0 Follow up of Adverse Events by Sponsor

Acknowledgement will be issued to the Investigator from the Sponsor via email within 7 days of receipt of a fully completed form, and this must be filed in the TMF/ISF.

Each SAE/SADE will be registered on the recognised Sponsor database and reviewed by the Sponsor or their delegate, as per Appendix 6 (Medical Device SAE/SADE review process flowchart). This review may lead to queries being issued by the Sponsor/delegate to request signed documentation, clarify information or complete event outcome. All queries will be sent via email and must be responded to within the stated timeframe.

All SAEs/SADEs reported to the Sponsor will be reviewed as part of a monthly line listing by the Director of R&I and are discussed at the Research Sponsorship Monitoring & Oversight Group (RSMOG). Events resulting in fatality and those considered related to the device/intervention are expedited to the Director of R&I and/or the insurance team as relevant.

8.0 Documentation

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

- SAE/SADE reports and follow-up information
- Adverse event/device effect document (Appendix 2)
- Evidence of submission and receipt of SAE/SADEs to the Sponsor and regulatory agencies within the required timeframe
- Evidence of timely notifications to the MHRA and main REC (where applicable)

The investigator must ensure that all SAE/SADE information is recorded accurately in the medical notes and the study CRF.

9.0 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.


10.0 Responsibilities

Responsibility	Undertaken by	Activity
CI/PI/Delegated individual	CI/PI/Delegated individual	Report all serious adverse events/device effects to the Sponsor (except those identified as exempt).
CI/PI/Delegated Individual	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 adverse event/adverse device effect record/and or line listing and review and sign off by Chief Investigator.
Sponsor	Sponsor or designee	Ensures that all reportable events are notified to the MHRA and REC within mandatory timelines.
CI/PI/Delegated individual	CI/PI/Delegated individual	Supply the Sponsor, MHRA and the main REC with any additional information requested.
Sponsor	Sponsor	Monitor all SAE/SADE line listings reported on a monthly basis to identify and if necessary act upon any emerging safety issues.
Sponsor	Research Quality Assurance Officer (RQAO)	The RQAO will review SAE/SADE submissions and request further clarification/information as required to ensure SAE/SADE report completion. The CI/PI will be provided with Sponsor acknowledgement of receipt of the completed SAE/SADE.

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

11.0 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 Management and Operations Group (RSMOG)	Professor Nigel Brunskill 	25/03/2024

12.0 Review Record

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

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
Sept 2021	1.1	Cat Taylor	Administrative changes.

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
March 2024		Cat Taylor	Addition of CE and UKCA to Section 2.0 definitions Minor updates to clarify the escalated review process of events Update to title of SOP Removal of legacy MORE portal instructions. Replaced with link to registration to and instructions for the new MORE portal. Minor updates to expectedness section to confirm expected events as those listed within the IB or CIP. Changed reference to SAE/SADE/USADE to SAE/SADE Removal of distribution record Appendix 2 – administrative changes Appendix 6 – administrative changes Removal of Appendix 5 -Device reporting form Removal of appendix 7 – template response email