Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

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Recording, Managing and Reporting Adverse Events in the UK for Medical Devices

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Author: Ruth Nicholson, Head of Research Governance and Integrity	
Approved by: Ruth Nicholson Head of Research Governance and Integrity	Date: 22 Feb 2021 Ruth Nicholson Digitally signed by Ruth Nicholson Date: 2021.02.23 10:54:45 Z

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Version 1.0	16 February 2021	New SOP

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1. PURPOSE

This SOP describes the process for recording, managing and reporting Adverse Events, including Adverse Event (AE), Serious Adverse Event (SAE), Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) or Unanticipated Serious Adverse Device Effect (USADE) for Imperial College Academic Health Science Centre (AHSC) sponsored studies of non-CE marked medical device studies, or CE marked devices used outside of their intended purpose which require MHRA approval.

2. INTRODUCTION

It is essential that all adverse events which occur during the course of study participants' involvement in a research project are appropriately recorded and reported in order to ensure their continuing safety.

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 14155:20020 (Clinical investigations of medical devices for human subjects – Good Clinical Practice)
- European Commission Guidelines on Medical Devices MEDDEV 2.7/3

Consequently, AEs can be classified into different categories (further explanations are given in section 2.1.)

1. Adverse Event
2. Adverse Device Effect (ADE)
3. Serious Adverse Event
4. Serious Adverse Device Effect (SADE)
5. Unanticipated Serious Adverse Device Effect (USADE)

Each type of AE is subject to different reporting requirements.

It is important that this SOP is followed as failure to report incidents, or deal with incidents adequately, can result in regulatory approval being withdrawn from an individual project, or, in extreme cases, from all research carried out by the Chief Investigator (CI) or Principal Investigator (PI).

2.1. Definitions

2.1.1. Investigational Medical Device

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

2.1.2. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons concerned with the medical device. These may, or may not be, considered related to the investigational device, device related procedure or comparator. If the AE is considered to have a reasonable causal relationship with the device, then it is considered to be an ADE.

2.1.3. Adverse Device Effect (ADE)

An Adverse Event (AE) related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation or operation of the medical device or any malfunction. This also includes any AE that is a result of an error in use or intentional misuse of the medical device.

2.1.4. Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device Deficiencies include malfunctions, misuse or use errors and inadequate labelling.

2.1.5. Serious Adverse Event (SAE)

An Adverse Event that results in:

- Death.
- Life threatening illness or injury.
- Permanent impairment of a body structure or body function.
- Hospitalisation or prolongation of existing hospitalisation.
- Medical or surgical intervention to prevent life threatening illness, injury or impairment to a body structure or body function.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator

This includes potential SAEs which were avoided as result of action or intervention. A planned hospitalisation for a pre-existing condition, or a procedure required in the protocol, without a serious deterioration in health, is not considered an SAE.

NOTE Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the serious adverse event reporting system.

Such adverse events should be reported as soon as possible. When reporting these events please include the total number of patients treated in the UK at the time of reporting.

Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious", which is based on patient/event outcome or action criteria.

2.1.6. Suspected Serious Device Effect (SADE)

An Adverse Device Effect (ADE) that results in:
- Death.
- Life threatening illness or injury
- Hospitalisation, or prolongation of existing hospitalisation.
- Persistent or significant disability or incapacity.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator

But has previously been identified in the Clinical investigators Plan and/or Investigator Brochure.

Any hospitalisation planned prior to enrolment is not a SADE.

2.1.7. Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

2.2. Responsibilities

There are a number of responsibilities when managing adverse events. Below is a list of responsibilities for both the Investigator and the Sponsor (for Imperial College AHSC sponsored studies, the Research Governance and Integrity Team (RGIT) will act on behalf of the Sponsor).

The CI has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the relevant Research Ethics Committee (REC).

The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI should be the same person. The PI is responsible for informing the CI, or the coordinating research team, of all adverse events that occur at their site following the guidelines below.

Any CI/PI who has agreed to undertake duties for SAE reporting delegated by the Sponsor must undertake both Investigator's and Sponsor's responsibilities as described throughout this document.

2.2.1. Investigator's Responsibilities

1. PI to report all SAEs within agreed timelines to the CI (see section 3.3)
2. CI to report all SAEs within agreed timelines to Sponsor
3. CI to report SAEs within agreed timelines to Sponsor, MHRA, REC and relevant NHS Trust Research and Development Office (R&D) (see section 3.3)
4. Provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
5. Review SAE reports from Investigators and perform an evaluation with respect to seriousness, causality and expectedness.
6. Supply the Sponsor, MHRA, REC and relevant NHS Trust R&D with any supplementary information they request.

2.2.2. Sponsor's Responsibilities

1. In collaboration with the Device Manufacturer, perform ongoing safety evaluation of the trial device and report any findings that may affect the health of subjects to the Device Manufacturer.
2. Promptly notify all Investigators, REC(s) and MHRA (if required), of any findings that may affect the health of subjects.
3. Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. Report all relevant safety information and SAEs to the relevant REC and MHRA within the relevant timelines
5. Break treatment codes before submitting expedited reports to MHRA and REC for specific subjects, even if the Investigator has not broken the code. (Note: A system for maintaining blinding for the CI/PI and trial staff may need to be agreed in advance).
6. Submit the annual report to Sponsor and REC.
7. Submit summary reports as required to the MHRA.

Note that for Imperial AHSC sponsored studies the above sponsor responsibilities are delegated to the CI.

3. PROCEDURES

3.1. Study Planning

All CIPs and/or IB should list known side effects and adverse reactions contained within the manufacturer's product information. This should be written in agreement with the relevant device company where applicable. Rare/very rare events may or may not be included depending on individual study requirements.

A detailed explanation of SAE reporting procedures should also be included in the protocol.

A generic SAE reporting form is available in Appendix 1: RGIT_TEMP_063 This form can be amended to create a study specific form following consultation with the RGIT.

3.1.1. Which AE to Record?

The CI can decide how to record and report adverse events, whether expected or not. Adverse events are usually described on case report forms (CRFs), unless they are classified as serious, in which case, these should be reported on a specific SAE form (see Appendix 1: RGIT_TEMP_063 or an example). It should be clearly stated in the study protocol and the local SOP what will be recorded and how the reporting is to be managed.

It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the trial and any safety and efficacy end points.

3.1.2. Which SAE to Report?

The management and reporting arrangements for SAEs should be in place for all trials. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.

It is recommended that an Independent Data Monitoring Committee (IDMC) is appointed in order to review safety data regularly throughout the trial and when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial. Again, this procedure must be defined in the protocol.

As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (2018) must be maintained on all reports.

3.2. During the Trial

Each AE must be evaluated for **seriousness** (see 2.1.4)**, causality, and expectedness**. The responsibility for this evaluation can be shared between the CI and PIs. It may be most appropriate for the treating PI at each local site to evaluate each event, before reporting it to the CI. It must be stated in the clinical trial protocol and the local SOP who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting may be required, this SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

3.2.1. Causality

Adverse reactions should be assessed for causality. The definitions below can be used.

Relationship	Description
Unrelated	There is no evidence of any causal relationship to the medical 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 device is weak but cannot be ruled out completely
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot be reasonably be explained by another cause.
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt.

If different causality definitions are specified in the protocol, it must be clear which definitions constitute a 'related' event.

3.2.2. Assessment of Expectedness

Expected: The reaction is consistent with the effects of the device listed in the Investigator Brochure (IB)or Clinical Investigation Plan (CIP)

Unexpected: the reaction is not consistent with the effects of the device listed in the IB and/or CIP.

3.3. Reporting Guidelines –non-CE Marked, or CE marked devices used outside of their intended purpose, MHRA approved Medical device studies

Once the CI/PI has evaluated the AE in terms of seriousness, causality and expectedness, the following guidelines should be followed.

3.3.1. AEs/ADEs

The CI can decide how to record and report adverse events. AEs that will be reported and are not considered serious should be included in the patient notes and on the relevant case report forms (CRFs). The completed form should be filed along with the other CRFs for the study. It should clearly be stated in the study protocol and the local SOP what will be recorded and how the reporting is to be managed. The options must be consistent with the purpose of the trial and trial end points.

3.3.2. SAEs/SADEs

If the AE is assessed as serious, the PI **must** report the event to the CI **immediately or within 24 hours** of being made aware of the event (other than those SAEs identified in the protocol as not requiring immediate reporting). The initial report can be made via email but must be promptly followed with a detailed, written report. The PI must record the event with his

assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the CI (see Appendix 1: RGIT_TEMP_063). The PI should ensure that follow-up information is provided when available. Where supporting documents are sent with this form, these must be pseudonymised. Where the information available is incomplete at that time, as much information as can be ascertained should be sent to ensure timely reporting, with additional information provided as soon as it is known. Additional information received for an event (follow-up or corrections to the original event data) needs to be detailed on a new SAE form

> **Follow-up of adverse events**
> All adverse events must be followed-up until resolution or death of the participant.

The letter of no objection from the MHRA will also detail whether summary reports (including their frequency) need to be submitted to the MHRA. The information to be submitted must be provided in tabular format as shown on the second tab of Appendix 4: RGIT_TEMP_064.

3.3.3. SAE reporting to MHRA

For trials of medical devices that are: non CE-marked or CE marked but are being used outside of the intended use(s) covered by the CE mark, the following must be reported to the MHRA by the delegated reporting form in Appendix 4: RGIT_TEMP_064.

a) Any SAE (whether initially considered to be device related or not)
b) Any Investigational Medical Device Deficiency that might have led to a SAE if,
    1. Suitable action had not been taken or
    2. Intervention had not been made or
    3. If circumstances had been less fortunate
c) New findings/updates in relation to already reported events

The CI should ensure that these are reported to the RGIT within 24 hours.
The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to the MHRA each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of the MHRA.

Please email the complete MEDDEV 2/7/3 reporting spreadsheet to aic@mhra.gov.uk quoting MHRA's CI reference number. SAEs which indicate an imminent risk of death, serious injury or serious illness and require prompt remedial action for other patients, users or other persons or a new finding to it, must be reported to the MHRA by the CI **immediately** but not later than **2** calendar days following the date the Sponsor is made aware, using the summary tabulation in Appendix 4: RGIT_TEMP_064.

Any other reportable events should be reported **immediately** but not later than **7** calendar days following the date the Sponsor is made aware, using the same summary tabulation.
The device manufacturer should also be informed within 24 hours of the SAE or device deficiency if indicated in the study's communication agreement.

The PI/CI must send all SAE reports to the Research Governance and Integrity Team, Imperial College AHSC immediately or within 24 hours after becoming aware of the event at the below address:

RGIT@imperial.ac.uk

Local research governance procedures at each site, e.g. NHS Trust, should also be followed.

3.3.4. USADEs

If an SAE is determined to be unexpected (not previously described in the IB and/or CIP) and related to the study device then it is considered an USADE.
For USADEs, in addition to reporting to the MHRA as described in the sections above, the CI must also report the event to the REC in the UK and make sure the event is reported to Ethics Committees in participating countries as required. Reports should be made to the REC within **15** days according to HRA website using the non-CTIMP SAE form Appendix 2: RGIT_TEMP_005 SAE reporting form for non-CTIMP (please refer to RGIT_SOP_001).
The Device Manufacturer and Investigators at all sites should be notified of the USADE.

Clinical Trials of Medical Devices are typically open-labelled studies. In some trials, e.g. a trial of an implantable active device, the patient might have the device implanted but allocated to treatment periods where the device is active or inactive. Unblinding might have to be considered in the event of a USADE, although unblinding should be avoided where possible.

3.3.5. Urgent Safety Measures

The Chief and Principal Investigators have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the RGIT, MHRA and REC within three calendar days of the occurrence. This may be reported verbally in the first instance but must be supported by a written report as soon as information is available. Please refer to RGIT_SOP_037.

3.4. Reporting Guidelines – CE marked medical devices or non-MHRA approved device studies

If a research participant experiences a SAE you should report this to the relevant Research Ethics Committee and the Research Governance and Integrity Team, Imperial College AHSC, where in the opinion of the chief investigator 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 as an expected occurrence.

For medical devices this means the USADEs should be reported

Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event, using the form in Appendix 2: RGIT_TEMP_005. The form should be completed in typescript and signed by the chief investigator.

Reports of double-blind studies should be unblinded.

3.5. Annual Reports

An annual progress report should be submitted to the REC which gave the favourable opinion 12 months after the date of the favourable opinion letter. The APR should be emailed to REC within 30 days of this reporting period.

3.6. Adverse Event Reporting for International Trials

Clinical trials that involve sites outside of the UK must follow the requirements of the countries in which the trial is taking place. SAEs should be reported as applicable to all member states in the study

The procedures for reporting relevant events onwards to regulatory and ethics committees should be included in any agreements between international groups performing the trial. The protocol and/ or study specific SOP should specify procedures for both the timing and format of reports of SAEs in sites outside the EU. SAEs in third countries should also report to member states if using the same clinical investigation plan.

3.7. Trend Analyses

The CI, in conjunction with the manufacturer should undertake trend analysis regarding the safety of the device.

4. REFERENCES

Data Protection Act (2018)
Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use

National Research Ethics Service guidance on safety reporting

MRC/DH joint project, Workstream 6: Pharmacovigilance

EU Regulations for medical devices

EC guidance on medical device directive

ED guidelines on Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC and 93/42/EEC

5. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Sample Medical Device SAE Form - RGIT_TEMP_063
Appendix 2: SAE Reporting Form for Non-IMP Studies – RGIT_TEMP_005

Appendix 3: MHRA Addresses

Please use the MEDDEV 2.7/3 reporting Excel spreadsheet to report serious adverse events. Please email the complete spreadsheet to aic@mhra.gov.uk quoting MHRA's CI reference number or upload through MORE AIC MHRA Website/ including the MHRA's CI reference number in the 'incident description' field. Please ensure that sufficient information is included in the table to allow MHRA to understand what happened in each incident and that all fields are complete. Failure to do so will result in further requests for additional information on each individual case, therefore please ensure the following:

a. ALL sections are completed in FULL, especially sections where a decision is required as to whether or not the event is device / procedure related.
b. Any deaths reported should have the cause of death recorded.
c. Reports should be made in a timely manner as per regulatory requirements.

Please note that adverse events involving a medicinal product should also be reported to MHRA Medicines by the manufacturer of the medicine or sponsor of the study. Information on the requirements for reporting of such events can be found here Yellow Card - MHRA

Appendix 4: Medical Device Report Form – RGIT_TEMP_064