Title: Adverse Events in Medical Device Clinical Investigations

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Document History

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<tr>
<th>Version</th>
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<tr>
<td>1</td>
<td>New SOP</td>
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<td>2</td>
<td>Scope amended to include CE-marked devices used within intended use Clarity of SAE reporting at 3.9 and 3.19 Reference to events considered medically significant at 4.3 and 4.4 Reference to SADEs avoided as a result of intervention at 4.4</td>
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<td>Scheduled review at three years. Reference to USADE at 4.5. Updated references at 3.14, 3.21 and 5 Clarification of Device Deficiencies at 3.8 Updated AE assessment and reporting process from 3.9 Reference to UKCA at 4.7</td>
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1. Scope

1.1 This SOP applies to any individual delegated the task of identifying, recording and reporting an Adverse Event (AE), Serious Adverse Event (SAE), Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) or Unanticipated Serious Adverse Device Effect (USADE) occurring in a Clinical Investigation of a medical device (CIMD) sponsored or co-sponsored by the University of Aberdeen (UoA) and/or NHS Grampian (NHSG).

1.2 This procedure applies to Non-CE marked devices and CE marked devices used outside the intended use(s) covered by the CE marking. Where appropriate this SOP may also be used for CE-marked devices used within their intended use(s).

1.3 For other interventional studies please contact the Research Governance Office for advice researchgovernance@abdn.ac.uk

2. Responsibilities

Chief Investigator (CI) Report, assess and sign-off Adverse Events occurring in Grampian.
Principal Investigator (PI) Report, assess and sign-off Adverse Events occurring outside Grampian.
Sponsor Ensuring SAEs, SADEs and USADEs are reported to the MHRA and REC.

3. Procedure

3.1 The decision on what SAEs to record and report should be determined during the trial protocol development and be informed by the CI and Sponsor risk assessment. This should also be noted for SAEs (which are a subset of AEs) particularly in relation to whether any will be recorded as outcomes rather than as SAEs.
3.2 AEs shall be recorded from the time the participant signs the informed consent form, unless otherwise defined in the protocol.

3.3 The protocol shall define how AEs will be identified. Unless otherwise stated in the protocol the Chief Investigator (CI), or delegate, shall enquire with the participant at each trial visit about any hospitalisations, consultations with medical practitioners, disability, incapacity or whether any other AEs have occurred.

3.4 AEs may also be identified by support departments (eg abnormal laboratory measurements). If notification of such abnormal results would not normally be communicated to the trial team then the procedure for doing so must be documented in the protocol.

3.5 Where the right to bear the CE mark has been obtained before the end of a trial the SAE reporting continues as stated in the protocol until completion.

Recording AEs, SAEs and Device Deficiencies

3.6 The protocol shall define what AE data points shall be recorded. The appropriate AE and SAE pages of the Case Report Form (CRF) can be designed appropriately to capture this data.

3.7 Unless stated in the protocol AEs and SAEs shall be followed up until resolution, or death of the participant.

3.8 If the AE or SAE occurred because of a device deficiency, the Medical Device deficiencies/User Error report should also be completed.

Assessment of AEs

3.9 Each AE must be assessed for seriousness, causality, severity and expectedness by the Chief Investigator (CI) within Grampian, or Principal Investigator (PI) if outside Grampian. This responsibility may be delegated by the CI or PI to another Consultant at that site if required. This must be documented in the Site Delegation Log (TMP-QA-13).

3.10 The local PI, or delegate, must report SAEs in a timely manner (within 24 hours of knowledge of event) to the CI. All SAEs must be recorded on the MEDDEV SAE reporting table.

3.11 The Investigator shall make an assessment of seriousness (see section 4) and whether an AE is likely to be related to the device and/or procedure as follows:

Not related: where relationship to the device and/or procedure can be excluded.
Unlikely: where the relationship with the use of the device seems not relevant and/or the AE can be reasonably explained by another cause, but additional information may be obtained.
Possible: where the nature of the event, underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the device. Cases where relatedness cannot be assessed or no information has been obtained, shall also be classified as possible.
Probable: where relationship with use of the device seems relevant and/or the AE cannot reasonably be explained by another cause, but additional information may be obtained.
Causal: where the AE is associated with the device and/or procedure beyond reasonable doubt.

If the Sponsor and investigator have a different opinion both shall be documented.
3.12 The Investigator shall make an assessment of severity and record in the CRF, as follows:

**Mild**: an event easily tolerated by the participant, causing minimal discomfort and not interfering with daily activities.

**Moderate**: an event that is sufficiently discomforting to interfere with normal daily activities.

**Severe**: an event that prevents normal daily activities.

⚠️ The term ‘severe’ is used to describe the intensity of the event and must not be confused with ‘serious’; a regulatory definition based on participant or event outcome (e.g., a headache may be severe but not serious, whilst a stroke may be serious but is not severe).

3.13 If an AE is judged to be related to the device, the Investigator shall make an assessment of expectedness based on knowledge of the reaction and any relevant product information. The event shall be classed as follows:

**Expected**: the reaction is consistent with the effects of the device listed in the risk analysis report.

**Unexpected**: the reaction is not consistent with the effects of the device listed in the risk analysis report and has never been previously documented.

### Reporting SAEs, SADEs, USADEs and Device Deficiencies to the Sponsor

3.14 The above are subject to expedited reporting to Sponsor, this includes post-study USADEs that occur after a participant has completed a clinical investigation. SAEs, SADEs and USADEs shall be documented on the Medical Device Vigilance report (TMP-QA-52). Device Deficiencies shall be documented on the Medical Device Deficiencies/User Error report (TMP-QA-53).

3.15 ⚠️ All SAE, SADE, USADE and Device Deficiency reports must be notified to Sponsor (using pharmaco@abdn.ac.uk) **within 24 hours** of the CI, or delegate, becoming aware. All such reports to Sponsor must be signed by the investigator and provide an assessment of causality.

⚠️ Initial reporting to sponsor must not be delayed if there is any issue in obtaining a signature by the investigator and/or assessment of causality.

3.16 Where any information is missing from the initial SAE, SADE, USADE or Device Deficiency report the Research Governance Team shall contact the investigator to obtain additional information.

3.17 ⚠️ The Research Governance Manager, or delegate, shall ensure all Device Deficiency Reports, including any additional information, is filed in the Sponsor file once complete.

### Reporting of SAEs to Research Ethics Committee and Competent Authority

3.18 The Research Governance Team, or nominated delegate, is responsible for reporting of SAEs, SADEs, USADEs and Device Deficiencies (which may potentially have resulted in an SAE) to the Research Ethics Committee and Competent Authority.

3.19 ⚠️ Any SAEs which indicate an imminent risk of death, serious injury or serious illness, and which requires prompt remedial action for other subjects, shall be reported within **two calendar days** of awareness by Sponsor. Any other SAEs shall be reported within **seven calendar days** of Sponsor awareness.

3.20 The SAE report must be provided to the National Competent Authorities relevant to all states in which the clinical investigation is taking place. The National Competent Authority for the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). The report shall be made using the MEDDEV 2.7/3 SAE reporting table ([https://www.abdn.ac.uk/clinicalresearchgovernance/sops/index.php](https://www.abdn.ac.uk/clinicalresearchgovernance/sops/index.php)).

**Uncontrolled when printed. Please ensure that you are working on the most up to date version of this SOP.**

**Key to symbols**

⚠️ = Important point to note  
⚠️ = Warning
4. Abbreviations and definitions

**Adverse Device Effect (ADE)**
4.1 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, installation or operation of the medical device or any malfunction.
- This also includes any AE that is a result of a use error or intentional misuse of the medical device.
- This includes any comparator if the comparator is a medical device.

**Adverse Event (AE)**
4.2 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.

**Serious Adverse Event (SAE)**
4.3 An Adverse Event that results in:

- Death.
- Serious deterioration in the health of the subject that either resulted in:
  - A life threatening illness or injury*;
  - permanent impairment of a body structure or body function;
  - in-patient or prolonged 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 anomaly or birth defect.

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

*Where the participant was at risk of death at the time of the event, which were avoided as result of action or intervention. Not an event which hypothetically might have caused death if more severe.
**Any hospitalisation which was planned prior to enrolment in the study is **not** a SAE.

**Serious Adverse Device Effect (SADE)**
4.4 An Adverse Device Effect (ADE) which has resulted in any of the consequences listed at 4.3

**Unanticipated Serious Adverse Device Effect (USADE)**
4.5 A Serious Adverse Device Effect which by its nature, incidence, severity or outcome has **not** been identified in the protocol or risk assessment as an Anticipated Serious Adverse Device Effect (ASADE) and is previously undocumented.

**Device Deficiency**
4.6 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.

**UKCA/CE Marking**
4.7 Medical devices cannot be sold in the UK or Europe without a UKCA and/or CE mark. The UKCA/CE mark is a manufacturer’s declaration that the product complies with the essential requirements of the
relevant European health, safety and environmental protection legislation. UKCA/CE marking indicates to government officials that a product may be legally placed on the market in their country.

4.8 Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>ADE</td>
<td>Adverse Device Effect</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ASADE</td>
<td>Anticipated Serious Adverse Device Effect</td>
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<td>CE</td>
<td>Conformité Européene (European Conformity)</td>
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<td>CIMD</td>
<td>Clinical Investigation of a Medical Device</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>REC</td>
<td>Research Ethics Committee</td>
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<td>SADE</td>
<td>Serious Adverse Device Effect</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>UKCA</td>
<td>United Kingdom Conformity Assessment (from 1 January 2021)</td>
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<td>USADE</td>
<td>Unanticipated Serious Adverse Device Effect</td>
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5. Related documentation and references

- SOP-QA-3 Protocol guidance for high risk trials and CTIMPs
- SOP-QA-6 Study start-up
- SOP-QA-31 Research project closure
- TMP-QA-12 Pregnancy notification form
- TMP-QA-13 Site delegation log
- TMP-QA-52 Medical Device Vigilance report
- TMP-QA-53 Medical Device Deficiency/User Error report
- Medical Devices Regulations (SI 2002/618) as amended
- EU MEDDEV 2.12-1 R8 European Commission Guidance Document on a medical devices vigilance system