

# SOP-QA-39 V4

## Title: Adverse Events in Medical Device Clinical Investigations

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GRAMPIAN CLINICAL RESEARCH OFFICE



### Document History

Version	Description of update	Date Effective
3	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	3-12-20
4	Reference to UKCA marking in addition to CE marking throughout Reference to CIP throughout Reference to Serious Health Threat at 1.1 and 4.5 Reference to anticipated or unanticipated AE at 4.2	20-12-23



### 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), Unanticipated Serious Adverse Device Effect (USADE) or Serious Health Threat** occurring in a Medical Device Clinical Investigation (MDCI) sponsored or co-sponsored by the University of Aberdeen (UoA) and/or NHS Grampian (NHSG).
- 1.2 This procedure applies to Non-CE/UKCA marked devices and CE/UKCA marked devices used outside the intended use(s) covered by the CE/UKCA marking. Where appropriate this SOP may also be used for CE/UKCA-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](mailto: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 Clinical Investigation Plan (CIP) development and be informed by the Chief Investigator (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 CIP.

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- 3.3 The CIP shall define how AEs shall be identified. Unless otherwise stated in the CIP the 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 CIP.
- 3.5  Where the right to bear the CE/UKCA mark has been obtained before the end of a trial, the SAE reporting continues as stated in the CIP until completion.

#### Recording AEs, SAEs and Device Deficiencies

- 3.6 The CIP 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 CIP, 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 Principal Investigator (PI). 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 or Trial Office, as described in the CIP.
- 3.11 The local PI, or delegate, 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 local PI, or delegate, shall make an assessment of severity, 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.

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⚠ 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 (eg 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 local PI, or delegate, 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 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.

3.14 ⚠ Sponsor shall perform risk analysis with the CI and manufacturer (if required) to determine if the information about AEs or Device Deficiencies is reflected in the current risk assessment and if the risk remains acceptable.

3.15 ⚠ If the risk is classed as possibly unacceptable, the risk assessment shall be updated and shall have one of four outcomes:

- Risk remains acceptable
- Corrective actions identified, and implemented which do not affect validity MDCI continues.
- Corrective actions identified which would affect validity of MDCI and investigation terminated.
- No corrective action may be applied and MDCI is terminated.

If the risk is classed as unacceptable and/or a Serious Health Threat is identified, Sponsor shall suspend the MDCI immediately.

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

3.16 The above are subject to expedited reporting to Sponsor, this includes post-study USADEs that occur after a participant has completed a MDCI. SAEs, SADEs and USADEs shall be documented on the SAE reporting form (TMP-QA-10). Device Deficiencies shall be documented on the Medical Device Deficiencies/User Error report (TMP-QA-53).

3.17 ⚠ All SAE, SADE, USADE and Device Deficiency reports must be notified to Sponsor (using [pharmaco@abdn.ac.uk](mailto: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.

3.18 Where any information is missing from the initial SAE, SADE, USADE or Device Deficiency report Sponsor shall contact the local PI, or delegate, to obtain additional information.



3.19 ⚠ The Sponsor shall ensure all Vigilance Reports, including any additional information, is filed in the Sponsor file once complete.

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

3.20 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.




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- 3.21  Any SAEs or Device Deficiencies 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 or Device Deficiencies, shall be reported within **seven calendar days** of Sponsor awareness.
- 3.22  The SAE report must be provided to the National Competent Authorities relevant to all states in which the MDCI is taking place. The National Competent Authority for the UK is the Medicines and Healthcare products Regulatory Agency (MHRA).

#### 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 includes any AE that is a result of 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 investigational medical device, and whether anticipated or unanticipated. 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 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.

\*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

##### Serious Health Threat

- 4.5 A signal from any AE or Device Deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or persons, and that requires prompt remedial action for other subjects, users or persons. This would include events that are of significant and

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unrelated nature, and such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

#### **Unanticipated Serious Adverse Device Effect (USADE)**

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

#### **Device Deficiency**

4.7 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**

4.8 Medical devices cannot be placed on the market 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/UK 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.

- CE marking remains acceptable in GB for general medical devices compliant with *EU Medical Devices Directive* or *EU Active Implantable Medical Devices Directive* until the sooner of CE certificate expiry or 30 June 2028.
- CE marking remains acceptable in GB for in vitro diagnostic medical devices compliant with *EU In Vitro Diagnostic Medical Devices Directive* until the sooner of CE certificate expiry or 30 June 2030.
- CE marking remains acceptable in GB for custom made devices compliant with *EU Medical Devices Regulation* and in vitro devices compliant with *EU In Vitro Diagnostic Medical Devices Regulations* until the sooner of CE certificate expiry or 30 June 2030.

#### **4.8. Abbreviations**

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CE	Conformité Européene (European Conformity)
CIP	Clinical Investigation Plan (Protocol)
CRF	Case Report Form
MDCI	Medical Device Clinical Investigation
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
UKCA	United Kingdom Conformity Assessment***
USADE	Unanticipated Serious Adverse Device Effect

\*\*\*Applies to Scotland, England and Wales (GB) only and is not recognised in EU, EEA or Northern Ireland.

#### **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

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TMP-QA-10	SAE reporting form
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
-	UK Medical Devices Regulations (SI 2002/618) as amended
EU MEDDEV 2.12-1 R8	European Commission Guidance Document on a medical devices vigilance system
ISO 14155:2020	Clinical investigation of medical devices for human subjects – Good clinical practice

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