STANDARD OPERATING PROCEDURE

Title | Adverse Event Reporting in Clinical Medical Device Trials
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Author(s) | Teresa O’Leary Head of Regulatory Compliance (Interim)
Reviewer(s) | Melanie Boulter, QA Auditor

Authorisation (Original signatures are retained by Research & Innovation)

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<th>Name</th>
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| Dr Brian Thomson  
Director of Research & Innovation | 24th Nov 2015 |
| Dr Stephen Fowlie  
Medical Director | 01th Dec 2015 |

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1. Document History

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Issue Date</th>
<th>Reason for Change</th>
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<tbody>
<tr>
<td>1</td>
<td>08th Dec 2015</td>
<td>Original SOP, replaces SOP-52</td>
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2. Introduction

In order to comply with the Clinical Investigation of Medical Devices for human subjects - Good Clinical Practice ISO 14155:2011, and the Medical Devices Regulations 2002, it is important that all researchers are aware of the different definitions related to adverse events in research, and how to record, report and review each of these specific occurrences. It is essential that all adverse events which occur during the course of a study are recorded and reported appropriately in order to ensure that patient safety is maintained. Adverse events are reportable from the time of study enrolment. For medical device trials the time of enrolment is defined as the time at which, following recruitment, a subject signs and dates the informed consent form.

Adverse events relating to trials involving medical devices can be classified into different categories (Further information on these categories is provided in section 4):

- Adverse event (AE)
- Adverse Device Effect (ADE)
- Serious Adverse Device Effect (SADE)
- Serious Adverse Event (SAE)
- Anticipated Serious Adverse Device Effect (ASADE)
- Unanticipated Serious Adverse Device Effect (USADE)

Investigator assessment of causality and expectedness is of particular importance.

3. Purpose and Scope

This SOP is applicable to all researchers undertaking projects that fall within the Clinical Investigation of Medical Devices for human subjects - Good Clinical Practice ISO 14155:2011 and the Medical Devices Regulations 2002 that are sponsored by Nottingham University Hospitals NHS Trust, where the study involves Non-CE marked devices or CE marked devices that are being used outside the intended use(s) covered by the CE marking.

Studies which do not fall under the scope of this SOP are Clinical medical device studies managed by a third party (e.g. NCTU) and where a specific safety reporting procedure has been agreed with NUH R&I (sponsor).
4. Responsibilities

All Research Staff
For NUH sponsored Clinical Medical Devices studies, any researcher who is delegated AE recording and reporting duties on the delegation log must comply with this SOP. For all studies, the researcher delegated this responsibility should also ensure, where appropriate, the AE is reported via the NUH Datix system if the event has occurred at NUH (refer to the NUH NHS Trust - Incidents Reporting Policy and Procedures Manual 2009).

Chief Investigator (CI)
Responsible for discussing AE information with researchers, including for multi-site CMDs, in accordance with this SOP.

Sponsor (fulfilled by the Research and Innovation (R&I) department on behalf of NUH)
Responsible for ensuring an independent assessment of AEs is performed as required, and that any AEs that require expedited reporting are reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) appropriately, and disseminated to all researchers in multi-site CMDs.

5. Definitions

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.
NOTE 1- 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.
NOTE 2- This includes any event that is a result of a use error or intentional misuse.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
NOTE 1: This includes events related to the investigational device or the comparator.
NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.
**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 risk analysis report or Clinical Investigation Brochure.

**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.

**Medical device**

A medical device is any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article:

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:

1. Diagnosis, prevention, monitoring, treatment or alleviation of disease,
2. Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
3. Investigation, replacement, modification, or support of the anatomy or of a physiological process,
4. Supporting or sustaining life,
5. Control of conception,
6. Disinfection of medical devices, and

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

N.B: The term “medical device” is usually defined by national regulations. For the purposes of this International Standard, this definition does not list “in vitro diagnostic medical devices” (see ISO 13485:2003, definition 3.7[1]).

**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.

**Serious Adverse Device Effect (SADE)**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Serious Adverse Event (SAE)**

Adverse event that:
a) led to a death,
b) led to a serious deterioration in health that either:
   1) resulted in a life-threatening illness or injury, or
   2) resulted in a permanent impairment of a body structure or a body function, or
   3) required in-patient hospitalization or prolongation of existing hospitalization, or
   4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

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

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.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

AE Adverse Event
ADE Adverse Device Effect
AE Adverse Event
ASADE Anticipated Serious Adverse Device Effect
CI Chief Investigator
CIB Clinical investigation Brochure
CIP Clinical Investigation Plan
ICH-GCP International Conference on Harmonisation Guidelines for Good Clinical Practice
ISF Investigator Site File
MHRA Medicines and Healthcare products Regulatory Agency
NCTU Nottingham University Clinical Trials Unit
NHS National Health Service
NHSP Nottingham Health Science Partners
NUH Nottingham University Hospitals NHS Trust
PI Principal Investigator
QA Quality Assurance
6. Procedure

6.1 Identification and recording Adverse Events

- The research site must protect the dignity, rights, safety and well-being of participants as a priority at all times. The Investigator (or other delegated researcher) must identify if an AE has occurred, as defined by the Clinical Investigation Plan (CIP). This is usually achieved through discussion with the participant during trial visits, but may also be identified if the researcher reviews the participant’s medical records or is informed by the participant’s relative, carer, another clinician or support department of an occurrence that would constitute such an event.

- If an AE has occurred the Investigator (or other delegated researcher) must review all relevant documentation (e.g. medical notes, laboratory results and diagnostic reports). The Investigator (i.e. medically qualified researcher) will assess the intensity, causality, expectedness and seriousness of the event as described in section 6.2.

- Unless stated otherwise in the CIP, all AEs must be recorded in detail. The research site must record all AEs using the Adverse Events Record (TAFR01901) and retain it with the participant’s Case Report Form (CRF), unless an AE record is incorporated into the CRF design and agreed by the Sponsor in which case this must be completed.

- The AE, including its severity, cause and seriousness, must also be recorded in the participant’s medical notes by the Investigator (or other delegated researcher).

- The CI (or Principal Investigator (PI) in multi-centre research) must review all recorded AEs at their site, and this must be documented on the Adverse Events Record (TAFR01901) and made available to the Sponsor on request.

- AEs and/or laboratory abnormalities defined in the protocol as critical to the evaluation of safety shall be reported to the Sponsor by the research site in accordance with the reporting requirements detailed in the protocol.
6.2 Assessment of AEs

- Each AE must be assessed for seriousness, causality, severity and expectedness. It is the Investigator(s) responsibility to assess each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

6.2.1 Assessment of Seriousness

- The Investigator should make an assessment of seriousness as defined in section 5.

6.2.2 Assessment of Causality

- The relationship between the investigational medical device and the occurrence of each adverse event will be assessed and categorised.
- The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. will be considered. The Investigator will also consult the current version of the risk analysis report and/or investigator brochure where available.

<table>
<thead>
<tr>
<th>Causality assessments</th>
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<tbody>
<tr>
<td>Relationship</td>
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</table>
| Not related: | No relationship with investigational device.  
| | Other factor(s) certainly or probably causative. |
| Related: | Temporal relationship of the onset of the event, relative to use of the device, is reasonable and there is no other cause to explain the event. |

- Where there are two assessments of causality, for example, the Investigator and the Sponsor assessment, or the CI and Investigator assessment, the causality made by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the most conservative assessment is used for reporting purposes. However, if the Sponsor’s disagrees with the investigators causality assessment then both opinions should be reported and fully documented.
6.2.3 Assessment of Severity

- The Investigator should make an assessment of severity for each AE and this should be recorded on the CRF or AE form according to the following categories:
- The intensity of an adverse event will initially be assessed according to the following definitions:

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mild</td>
<td>An event easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities</td>
</tr>
<tr>
<td>Moderate</td>
<td>An event sufficiently discomforting to interfere with normal everyday activities</td>
</tr>
<tr>
<td>Severe</td>
<td>An event that prevents normal everyday activities</td>
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6.2.4 Assessment of Anticipation

- Once an AE is deemed serious and device or procedure related it then must be assessed to determine if the SAE is “Anticipated” or “Unanticipated”.
- The Investigator should make an assessment of anticipation as defined in section 5.

6.2.5 Categorisation

The following table summarises categorisation of adverse events:

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Non-device related</th>
<th>Device or procedure related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-serious</td>
<td>Adverse Event (AE)</td>
<td>Adverse Device Effect (ADE)</td>
</tr>
<tr>
<td>Serious</td>
<td>Serious Adverse Event (SAE)</td>
<td>Serious Adverse Device Effect (SADE)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticipated</th>
<th>Unanticipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated Serious Device Effect (ASADE)</td>
<td>Unanticipated Serious Device Effect (USADE)</td>
</tr>
</tbody>
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6.3 Quarantine Devices

- If the event is defined as serious (SAE) or device deficiency that could have led to (U)SADE then the Investigator must quarantine the device as soon as possible.
- Until the MHRA has been given the opportunity to carry out an investigation, the device should not be:
  - discarded
  - repaired
  - returned to the manufacturer
- 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 any 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 local supplies of the device should be quarantined as a precaution until further advice is sought.

6.4 Reporting of SAE, SADE or USADE to Sponsor (NUH R&I)

- If the research site determines that an AE fulfils the criteria of an SAE or device deficiency that could have led to (U)SADE (as defined in the CIP and IB) the Investigator (or other delegated researcher) must report the SAE or (U)SADE to NUH R&I without unjustified delay. The only exception to this is where the CIP identifies the event as not requiring immediate reporting. The SAE or (U)SADE must be recorded on the Serious Adverse Events Log (TAFR01902) and retained in the ISF.
- The research site must report the SAE to R&I in writing using the SAE Reporting Form (Medical Devices) (TAFR01908), providing as much information as possible. The reporting form must be completed legibly ensuring that names, dates, and descriptions are clear and that abbreviations have not been used. For details of definitions required in the SAE reporting form, refer to section 6.2. The SAE may be reported verbally (but not by voicemail) in circumstances where a written report is not immediately possible; however this must be followed by a written report the next working day. SAE reports must be retained in the ISF.
• The CI (or PI in multi-centre research) must review and sign all SAE reports. In the event the CI/PI is unable to sign the report immediately the research site must not delay sending the report to R&I, however a CI/PI signed copy must be forwarded to R&I as soon as possible.
• The SAE form must be completed in full, entering N/A for questions which are not relevant.
• SAE reports must be sent to R&I using one of the following methods:
  i. Email (RDSAE@nuh.nhs.uk)
  ii. Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)
  iii. Telephone (0115 9709049) if written report not immediately possible
• For faxed SAEs an R&I representative who receives the SAE will provide a printed copy of the SAE report to the R&I RPM for the study immediately.
• For emailed SAEs, the R&I RPM for the study will check the group inbox daily.
• For hand delivered SAE reports the CI/PI (or delegate) must record the date and time the SAE was reported in the ‘Additional Comments’ section of the SAE Reporting Form (Medical Devices) (TAFR01908).
• For telephone reporting of SAEs:
  o R&I representative must complete a SAE Reporting Form (Medical Devices) (TAFR01908) with the details provided. In the ‘Additional Comments’ section, the R&I representative must record who received the call along with the date and time of the telephone call. The SAE form must then be reported to the Head of Regulatory compliance or R&I RPM immediately for further processing.
  o The CI/PI (or delegate) who telephones in an SAE must follow-up and complete a SAE Reporting Form (Medical Devices) (TAFR01908) and send the form to R&I via email or fax or hand delivery. The R&I RPM will collate and reconcile both SAE forms.
• The R&I RPM will check the SAE report for completeness, assign the SAE a unique reference number and ensure it is documented within the Serious Adverse Events Tracker (TAFR01907).
• The R&I RPM will send confirmation of receipt of the SAE report and its unique reference to the research site within 1 working day. Any omitted information or discrepancies will be requested from the research site.
• The research site must telephone R&I (0115 9709049) if the SAE reference number and confirmation of receipt is not received within 1 working day of sending the SAE report.
• The research site must provide any information omitted from the initial SAE report to R&I within a timely manner.
• The R&I RPM will facilitate an independent assessment of the event within 1 working day of receiving the SAE report.
• The independent assessment for causality and anticipation of the SAE will be performed by the Sponsor’s Medical Monitor within 24 business hours of their receipt, using the CIP or IB. The Medical Monitor will return the completed assessment to the R&I RPM.
• The R&I RPM will provide the CI with details of the SAE (if not already aware), update the Serious Adverse Events Tracker (TAFR01907) and retain all SAE documentation in the Trial Master File (TMF).
• The R&I RPM will provide a copy of the SAE follow up information to the Sponsor’s Medical Monitor and the CI (if not already aware), update the Serious Adverse Events Tracker (TARF01907) and retain the follow up documentation with the original SAE documentation in the TMF within R&I.
• For further reporting purpose:
  In the case of a difference of opinion, both assessments are recorded and the most conservative assessment is used for reporting purposes. However, if the Sponsor’s disagrees with the investigators causality assessment then both opinions should be reported and fully documented.

6.5 Reporting to the research ethics committee:

• If the event is classified as an SAE the investigator must report to the research ethics committee (REC).
  • SAE reports must be sent to R&I using one of the following methods:
    ▪ Email (RDSAE@nuh.nhs.uk)
    ▪ Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)
    ▪ Telephone (0115 9709049) if written report not immediately possible

• If the investigator classifies the event as a (U)SADE; the investigator must report the event to REC within 24 hours of becoming aware of the event.

6.6 Reporting of SADE or USADE to the regulatory authority:

• If the event is classified as a (U)SADE, then the sponsor (fulfilled by the R&I department on behalf of NUH) are responsible for reporting the SADE or USADE to the regulatory authority without unjustified delay.
• R&I RPM will inform the device manufacturer of the event. The device should not be returned to the manufacturer until the MHRA have completed their investigation.
• R&I RPM will inform the medical device liaison officer at NUH, this is the Head of Clinical Engineering.
• If the study is multicentre R&I RPM will inform all Principal Investigators involved in the study about the event.
6.7 Follow on Reporting

- After the initial report the investigator is required to actively follow up the subject until either:
  - The SAE/USADE resolves, or
  - Until 30 days after the discontinuation of use of the medical device.
- This decision must be documented in the TMF (for NUH sponsored studies) & Site file. Investigators (or delegated persons) will provide follow-up information, each time new information is available.
- Follow-up information must be reported using the TAFR01909_Serious Adverse Event Follow Up Report (CMDs) and must be submitted to R&I by either of the following methods:
  - Email (RDSAE@nuh.nhs.uk)
  - Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)
  - Telephone (0115 9709049) if written report not immediately possible
- The R&I RPM will forward a copy of the Follow-up report to CI and/or Medical Monitor (if required).
- The R&I Head of Regulatory Compliance, or delegated individual, will liaise with the investigator to gain an update regarding the progress of the SAE/USADE every two weeks until either:
  - The SAE/USADE resolves, or
  - Until 30 days after the discontinuation of use of the medical device.

6.8 Follow on action required from the MHRA investigation

- The investigator and NUH R&I will undertake any requirements outlined in the MHRA investigation and follow up as instructed.

6.9 Datix

- If applicable, SAEs, SADE or USADE which occur within NUH, must be reported on the Trusts electronic incident reporting system, Datix as well as to the Sponsor of the trial.
- Reporting of incidents on Datix must be carried out in accordance with the Trust's Incident Reporting Policy and Procedures Manual 2009.
6.10 Duty of Candour

- Duty of Candour is a new statutory requirement which applies to all providers (including NUH) registered with the CQC.
- Duty of Candour was recommended following the Mid-Staffordshire inquiry and was transposed into law to ensure openness and transparency with patients when an incident surrounding their care has occurred.
- All incidents which have been entered onto Datix (see 6.7) as moderate, severe or death (where the death relates directly to the incident) will be required to follow the Duty of Candour process.
- The requirement ensures that the appropriate information surrounding the incident is disseminated to patients, their relatives and carers.
- The Duty of Candour Trust SOP and flowchart should be followed for such events by formally following any information up in writing, should the patient, relative or carer request this.

7. References and Associated Documents

Clinical Investigation of Medical Devices for human subjects - Good Clinical Practice ISO 14155:2011
Medical Devices Regulations 2002
NUH Incident Reporting Policy and Procedures Manual, 2009

TAFR01901 Adverse Events Record
TAFR01907 Serious Adverse Events Tracker
TAFR01908 SAE Reporting Form (Medical Devices)
TAFR01902 Serious Adverse Events Log
TAFR01909 Serious Adverse Events Follow Up Form
### 8. Appendices

#### Appendix 1: Reporting process

**AE or ADE of causal relationship to device identified occurs**

- **Is AE/ADE serious?**
  - **Yes**
    - **If SAE; e-mail:** rdsae@nuh.nhs.uk or fax 0115 8493295
    - **If (US)ADE;** Report immediately to REC within 24 hours of becoming aware of the event; safety reporting form (non-climp): [http://www.nres.npsa.nhs.uk/applications/afterethicalreview/safetyreports/safetyreports-for-all-other-research/](http://www.nres.npsa.nhs.uk/applications/afterethicalreview/safetyreports/safetyreports-for-all-other-research/)
    - Copy in rdsae@nuh.nhs.uk or fax 0115 8493295
  - **No**
    - Log AE in medical records, or source data where this is not the medical records ie CRF. Record con med. Investigator to assess:
      - a) Causal relationship
      - b) Severity.

- **Has receipt of SAE/SADE confirmed by R&I?**
  - **Yes**
    - **Inform medical device liaison officer @NUH = Head of Clinical Engineering**
    - **Log SAE/SADE on DOCUMAS and in TMF.**
    - **Receive, file and log follow up reports until SAE/SADE resolved or until 30 days after discontinuation of use of medical device.**
    - **Generate reports of SAE/SADEs for as required.**
  - **No**
    - **Contact R&I immediately**
    - **Follow up until resolution or until 30 days after discontinuation of use of medical device.**

**SAE or device deficiency that could have led to (US)ADE**

- **Inform manufacturer**
- **Log SAE/SADE on DOCUMAS and in TMF.**
- **If multi-centre, inform all PIs.**
- **Report to MHRA.**
- **Await outcome of MHRA.**

- **If SAE or USADE**
  - **Log SAE/SADE on DOCUMAS and in TMF.**
  - **Inform medical device liaison officer @NUH = Head of Clinical Engineering.**

- **Has receipt of SAE/SADE confirmed by R&I?**
  - **Yes**
    - **Inform medical device liaison officer @NUH = Head of Clinical Engineering.**
    - **Log SAE/SADE on DOCUMAS and in TMF.**
    - **Generate reports of SAE/SADEs for as required.**
  - **No**
    - **Contact R&I immediately**
    - **Follow up until resolution or until 30 days after discontinuation of use of medical device.**

In addition the Investigator will review all laboratory reports and comment on any clinically important out of range values. All clinically important abnormal laboratory tests occurring during the trial will be repeated at appropriate intervals until they either return to baseline or to a level deemed acceptable by the Investigator and the Sponsor (or its designated representative), or until a diagnosis that explains them is made. *Clinically significant laboratory abnormalities should be reported as adverse events*. Out of range values that are not clinically significant should be marked ‘NCS’ on the laboratory report.

The investigator must sign and date all laboratory reports.