IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR CLINICAL INVESTIGATIONS OF MEDICAL DEVICES

1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 Adverse Event (AE) identification, recording and reporting procedures relating to trials involving medical devices where safety reporting is specified in the protocol, will comply with the requirements of the Medical Device Regulations 2002/618 and Good Clinical Practice (GCP).

1.3 Where NHSL and/or UoE agrees to co-sponsor a Clinical Investigation of Medical Device (CIMD) with another organisation the responsibility for medical device vigilance must be agreed between both organisations before the trial commences and should be clearly documented in a clinical trial agreement or equivalent.

2 PURPOSE

2.1 To describe the procedure for identifying, recording and reporting AEs and other safety events occurring in CIMDs that are sponsored by NHSL and/or the UoE.

3 SCOPE

3.1 This SOP applies to clinical researchers participating in CIMDs sponsored by NHSL and/or the UoE. This SOP is also applicable to ACCORD members of staff responsible for medical device vigilance.

4 RESPONSIBILITIES

4.1 ACCORD will be responsible for medical device vigilance for CIMDs that are sponsored by NHSL and/or UoE. This responsibility may not be delegated to the Investigator.

4.2 The Investigator will be responsible for identifying and reporting AEs, SAEs, SADEs, USADEs and device deficiencies as detailed in this procedure.
5 PROCEDURE

5.1 Definitions

5.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a subject enrolled into a trial, including occurrences which are not necessarily caused or related to the investigational medical device.

5.1.2 Serious Adverse Event (SAE)

An adverse event is defined as serious if it:

a. Results in death,
b. Is a life-threatening* illness or injury
c. Requires hospitalisation^ or prolongation of existing hospitalisation
d. Medical or surgical intervention required to prevent any of the above
e. Leads to foetal distress, foetal death or consists of a congenital anomaly or birth defect
f. Is otherwise considered medically significant by the Investigator

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

* Life-threatening in the definition of an SAE refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^ Any hospitalisation that was planned prior to randomisation will not meet SADE criteria. Any hospitalisation that is planned post randomisation, will meet the SADE criteria.

5.1.3 Adverse Device Effect (ADE)

An ADE is an adverse event 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 a 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.
5.1.4 **Serious Adverse Device Effect (SADE)**
A SADE is an adverse event effect that has resulted in any of the consequences characteristics of a SAE (see section 5.1.2). This includes device deficiencies that might have led to a SAE if;
- Suitable action had not been taken
- Intervention had not been made
- If circumstances had been less fortunate

5.1.5 **Anticipated Serious Adverse Device Effect (ASADE)**
A serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report or Clinical Investigation Plan.

5.1.6 **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 or Clinical Investigation Plan.

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

5.2 **Identifying and Recording AEs and SAEs**

5.2.1 The decision on what AE data to record will be the result of an assessment of the risk associated with the study before the trial is undertaken.

5.2.2 The protocol will define:
- What AEs or SAEs are **not** to be recorded, notified and/or reported
- When AEs or SAEs will be identified

5.2.3 The protocol will also define how AEs will be identified. Unless otherwise stated in the protocol, the Investigator(s) (or a member of the research team with delegated responsibility to do so – such delegation must be captured in the study site delegation log) will ask research participants at each trial visit about any hospitalisations, consultations with other medical practitioners, disability or incapacity or whether any other adverse events have occurred.

5.2.4 AEs and SAEs should be recorded from the time the participant signs the consent form to take part in the trial, unless otherwise defined in the protocol.

5.2.5 AEs may also be identified by support departments, for example, clinical biochemistry, haematology, radiology. Where notification of such abnormal values or measurements would not occur as standard clinical practice, the procedure for notifying the Investigator of such adverse events must be clearly documented in the protocol or trial specific procedures.
5.3 Assessment of AEs

5.3.1 Each AE must be assessed for seriousness, causality, severity and expectedness by the Principal Investigator (PI) or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role. During PI absences appropriately qualified, experienced and trained site staff may assess causality and report SAEs if they have been delegated this task on the delegation log by the PI.

5.3.2 For randomised double blind studies, AEs will be assessed as though the trial participant was subjected to the device.

5.4 Assessment of Seriousness

5.4.1 The Investigator will make an assessment of seriousness (as defined in section 5.1.2 and 5.1.4).

5.5 Assessment of Causality

5.5.1 The Investigator will also make an assessment of whether the AE is likely to be related to the device according to the following definitions:
- **Unrelated**: where an event is not considered to be related to the device.
- **Possibly Related**: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the device.

5.5.2 Where there are two assessments of causality (e.g. between PI and Chief Investigator (CI)), the causality assessment by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the ‘worst case’ assessment is used for reporting purposes.

5.6 Assessment of Expectedness

5.6.1 If the AE is judged to be related to the device, the Investigator will make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented in the risk analysis report. The event will be classed as either:
- **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 listed in the risk analysis report.

5.7 Assessment of Severity
5.7.1 The Investigator will make an assessment of severity for each AE according to the following categories:

- **Mild**: an event that is easily tolerated by the research participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

5.7.2 The term ‘severe’ used to describe the intensity of an event should not be confused with the term ‘serious’, as defined in section 5.1.3 and 5.1.4, which is a regulatory definition based on trial participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

5.8 Reporting SAEs/SADEs/USADEs to the Sponsor (ACCORD)

5.8.1 Any AE that is assessed as an SAE, SADE or USADE is subject to expedited reporting requirements. Post-study USADEs that occur after the trial participant has completed a clinical trial are also notified by the investigator to the Sponsor.

The protocol will define and justify which SAEs will not be subject to expedited reporting to the Sponsor.

5.8.2 The Investigator is responsible for reporting SAEs to ACCORD within 24 hours of becoming aware of the event.

5.8.3 SAE, SADEs and USADEs reports will either be emailed as a .pdf file to Safety@ACCORD.scot; delivered in person to a member of the Pharmacovigilance team or faxed to ACCORD on +44 (0)131 242 9447 using Template report CR012-T01 SAE (Devices) Form and the Cover Sheet and Return Receipt (CR012-F01). Reports will be complete as far as possible and will be signed and dated by the Investigator.

5.8.4 SAE, SADE and USADE reporting to ACCORD should maintain the blind unless it is considered necessary to break the blind in the interest of trial participant safety

5.8.5 The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt (CR012-F01) or send an email to confirm receipt of the SAE, SADE or USADE report within 1 working day. If this email/fax is not received within 1 working day of sending the report to ACCORD, the Investigator must telephone ACCORD on +44 (0)131 242 3330 to check that the report has been received by ACCORD.
5.8.6 Once an SAE, SADE or USADE report is received by ACCORD it will be entered onto the ACCORD PhV database by the Research Governance Coordinator or designee.

5.8.7 All SAE, SADE and USADE reports emailed or faxed to ACCORD and any follow-up information and correspondence will be kept by the Investigator in the Investigator Site File (ISF) and by the Sponsor in the Sponsor File or Trial Master File (TMF) if held. See also 5.11 for further details regarding follow-up.

5.8.8 For multicentre studies, ACCORD will report SAEs, SADEs and USADEs, as required, to the CI/Trial Manager within agreed timelines.

5.8.9 If there is a contractual obligation, ACCORD will report any SAEs, SADEs or USADEs as required to the third party within the agreed timelines.

5.9 Reporting device deficiencies to the Sponsor (ACCORD)

5.9.1 Device deficiencies will be documented on CR012-T02 Medical Device Deficiency Form and will be reported to the sponsor in accordance with section 5.8.

5.9.2 On receipt of device deficiency reports, the Research Governance Coordinator, or designee, will assess the report to ensure the correct assessment has been made. In the case of the event meeting SAE, SADE or USADE criteria, the Research Governance Coordinator, or designee will ensure that all the correct reporting procedures have been followed.

5.9.3 The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt (CR012-F01) or send an email to confirm receipt of the Device deficiency report within 1 working day. If this email/fax is not received within 1 working day of sending the report to ACCORD, the Investigator must telephone ACCORD on +44 (0)131 242 3330 to check that the report has been received by ACCORD.

5.9.4 The Investigator is responsible for reporting device deficiencies to the relevant NHS Medical Physics department, if applicable.

5.9.5 Device deficiency reports emailed or faxed to ACCORD and any follow-up information and correspondence will be kept by the Investigator in the Investigator ISF and by the Sponsor in the Sponsor File or TMF if held. See also 5.11 for further details regarding follow-up.

5.9.6 For multicentre studies, ACCORD will report device deficiency reports, as required, to the CI/Trial Manager within agreed timelines.

5.9.7 If there is a contractual obligation, ACCORD will report device deficiencies, or as required, to the third party within the agreed timelines.
5.10 Expedited Reporting of SADEs, USADEs and device deficiencies to the Research Ethics Committee (REC) and the Competent Authority (CA)

5.10.1 ACCORD is responsible for reporting all serious adverse events, SADEs and USADEs, received from Investigators to the CA. In addition, ACCORD is responsible for reporting any serious adverse event that is related and unexpected (USADE) to the REC.

5.10.2 Any SAEs (SADEs)/USADEs - which indicate an imminent risk of death, serious injury or serious illness and that requires prompt remedial action for other subject/users or other persons - will be reported within 2 calendar days of awareness by the Sponsor(s). Any other SAEs (SADEs)/USADEs will be reported within 7 calendar days of the sponsor becoming aware. The report must be provided to all CA relevant to all states in which the clinical investigation is taking place. The report will be made using the reporting form found here: http://ec.europa.eu/DocsRoom/documents/16477/attachments/2/translations

5.10.3 For blinded studies the blind will be broken by ACCORD before USADEs are reported to the REC and CA.

5.10.4 In multi-centre studies the ACCORD office is responsible for informing Investigators at all participating sites of any reported USADEs and any other arising safety information. This can be delegated to a coordinating unit/group/individual. Reports sent directly to the Investigator regarding USADEs from other studies of the same device must be reviewed by the Investigator and acted upon if appropriate. All copies of such USADE reports must be kept in the ISF and TMF and copies sent to the ACCORD office for filing in the Sponsor File or TMF if held.

5.11 Follow-Up

5.11.1 After recording and reporting safety events, it is the responsibility of the Investigator to follow-up the affected participant(s) until resolution of the event or death of the participant(s).

5.11.2 If the outcome of an initial report of an event is one of the following outcome options:

- Condition still present and unchanged
- Condition deteriorated
- Condition improving

Then the Investigator must follow-up with the participant(s). Unless otherwise defined in the protocol, a safety report will not be considered complete until the outcome is:

- Completely recovered (including date of recovery)
-Recovered with sequelae (including date of recovery)
5.11.3 All new information/follow-up information must be initialled and dated on the follow-up reports.

5.11.4 Follow-up reports should be submitted to the sponsor (ACCORD) as per section 5.8 and 5.9.

5.12 External Contracting of SAE (SADE) and USADE Reporting

5.12.1 Expedited reporting may be contracted to an external facility for individual studies. Study specific expedited reporting will be detailed in the protocol.

5.13 Medical Device Quarantine

5.16.1 If the event is defined as serious i.e. a SAE or device deficiency that could have led to SADE or USADE the Investigator must quarantine the device as soon as possible e.g. segregating the device from other equipment and labelling as not for use with contact details attached.

5.16.2 Until the CA and Sponsor has been given the opportunity to carry out an investigation, all items (together with relevant packaging materials) should be quarantined. They should not be repaired, or discarded or returned to the manufacturer without agreement from the sponsor.

5.16.3 Medical devices should not be sent to the CA unless this has been specifically requested. Investigators should contact the manufacturer to obtain information relating to the procedure for returning the device, where considered appropriate.

5.16.4 The device should be cleaned and decontaminated where appropriate, securely packaged, and clearly labelled, including the CA or manufacturer reference number if needed. Documentation regarding shipment and receipt of the device, where available, will be retained in the ISF.

6 REFERENCES AND RELATED DOCUMENTS

- The Medical Device Regulations (SI: 2002/618) as amended
- ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects
- Guidelines on a Medical Devices Vigilance System – MEDDEV 2.12/1 rev.8
- CR012-T01 Medical Device Vigilance Form
- CR012-T02 Medical Device Deficiency Form
- CR012-F01 Cover Sheet and Return Receipt
- PV001 Pharmacovigilance: Receipt, Onward Reporting and Follow-Up of Safety Reports
7 DOCUMENT HISTORY

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<tr>
<th>Version Number</th>
<th>Effective Date</th>
<th>Reason for Change</th>
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<tbody>
<tr>
<td>1.0</td>
<td>14 SEPT 2011</td>
<td>N/A – new procedure</td>
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<tr>
<td>2.0</td>
<td>02 OCT 2017</td>
<td>Amended procedures to align with ACCORD internal procedures associated with PV001. The definitions at section 5.1. have been updated in line with ISO 14155:2011 and MEDDEV 2.12/1 rev.8. SOP now captures procedures for the assessment of AEs in PI absences. ACCORD contact details have been updated throughout the SOP. SOP now captures procedures for medical device quarantine and reporting device deficiencies to Medical Physics.</td>
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8 APPROVALS

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