IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS AND URGENT SAFETY MEASURES FOR NON-CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

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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) and other safety event identification, recording and reporting procedures will comply with the requirements of Good Clinical Practice (GCP).

1.3 Where NHSL and/or UoE agrees to co-sponsor a study with another organisation the responsibility for AE reporting must be agreed between both organisations before the study commences and should be clearly documented in an agreement or equivalent.

2 PURPOSE

2.1 To describe the procedure for identifying, recording and reporting AEs and urgent safety measures (USMs) occurring in non Clinical Trials of Investigational Medicinal Products (non-CTIMPs) that are sponsored by NHSL and/or the UoE.

3 SCOPE

3.1 This SOP applies to clinical researchers participating in studies sponsored by NHSL and/or UoE. This SOP is also applicable to ACCORD members of staff responsible for safety reporting following ACCORD SOP PV001.

4 RESPONSIBILITIES

4.1 The Investigator will be responsible for identifying and reporting AEs and other safety events as detailed in this procedure.

4.2 ACCORD will be responsible for AE reporting for non-CTIMP studies that are sponsored by NHSL and/or the UoE. This responsibility may not be delegated to the Investigator.

5 PROCEDURE

5.1 Definitions

5.1.1 Adverse Event (AE)

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

5.1.2 Adverse Reaction (AR)

Any untoward and unintended response that has occurred due to the intervention.

5.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any AE or AR that:

- results in death of the study participant
- is life-threatening*
- requires inpatient hospitalisation^ or prolongation of existing inpatient hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- results in any other significant medical event not meeting the criteria above

* Life-threatening in the definition of an SAE or SAR 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 SAE criteria. Any hospitalisation that is planned post randomisation, will meet the SAE criteria.

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 study is undertaken. There is no requirement for recording of AE data for non-interventional, non-invasive studies (i.e. questionnaire based studies).

5.2.2 For interventional studies, 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 AE and SAE data will be recorded by the Investigator(s) (or a member of the research team with delegated responsibility to do so) on the Case Report Forms (CRF) and/or SAE report form CR006-T01. Investigators will record all

AEs in the non-CTIMP AE log (CR006-T03), unless otherwise defined in the protocol. AE details will be entered into the AE log in a timely fashion.

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

5.2.5 AEs and SAEs will be followed up until outcome of recovered, recovered with sequelae or death of the study participant, unless otherwise defined in the protocol.

5.2.6 AEs or SAEs 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 study 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 responsibility on the delegation log by the PI.

5.3.2 For randomised double-blind studies, AEs will be assessed as though the study participant was randomised to the study intervention.

5.4 Assessment of Seriousness

5.4.1 The Investigator will make an assessment of seriousness (as defined in section 5.1.3).

5.5 Assessment of Causality

5.5.1 The Investigator will make an assessment of whether the AE is likely to be related to the study intervention according to the following definitions:

- Unrelated: where an event is not considered to have occurred as a result of the study intervention.
- 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 study intervention.

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 study intervention, the Investigator will make an assessment of expectedness.

- Expected: The type of event is expected in line with the study intervention.
- Unexpected: The type of event was not listed in the protocol or related documents/literature as an expected occurrence.

5.7 Assessment of Severity

5.7.1 The Investigator will make an assessment of severity for each AE and this should be recorded on the CRF or SAE form according to the following categories:

- Mild: an event that is easily tolerated by the study 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, which is a regulatory definition based on study 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 Information to be Collected

5.8.1 SAE reports must be as complete as possible at the time of initial reporting to ACCORD.

5.8.2 If any of the required information is not available at the time of reporting, the Investigator must ensure that any missing information is emailed or faxed to ACCORD as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event (see section 5.9 for reporting to ACCORD).

5.8.3 Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. If it is not possible to supply any further detail this will be recorded on the database.

5.8.4 If reports are received by ACCORD with identifiable data, the data will immediately be scored through by ACCORD and the sender informed of this

breach in confidentiality and that they must take steps to ensure that this does not reoccur, where appropriate.

5.9 Reporting SAEs to the Sponsor (ACCORD)

5.9.1 Any AE that is assessed as an SAE is subject to expedited reporting requirements to the Sponsor.

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

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

5.9.3 SAE reports will either be emailed as a .pdf file to Safety@ACCORD.scot; delivered in person or faxed to ACCORD on +44 (0)131 242 9447 using the Template CR006-T01 (Serious Adverse Event Report Form (non-CTIMP)) and the Cover Sheet and Return Receipt CR006-F01. SAE reports will be complete as far as possible and will be signed and dated by the Investigator.

5.9.4 SAE reporting to ACCORD should maintain the blind unless it is considered necessary to break the blind in the interest of study participant safety.

5.9.5 The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt (CR006-F01) or send an email to confirm receipt of the SAE 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.

5.9.6 Once an SAE report is received by ACCORD it will be entered onto the ACCORD pharmacovigilance (PhV) database by the Research Governance Coordinator, or designee.

5.9.7 All copies of SAE 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).

5.9.8 If required, the non-CTIMP SAE Follow-Up Sign Off Sheet (CR006-T04) should be completed alongside the original SAE form.

5.9.9 For multicentre studies, ACCORD will report SAEs, as required, to the Chief Investigator/Trial Manager within agreed timelines.

Template CR006-T02 (Adverse Event Flowchart - Reporting) illustrates the reporting procedure and can be used by investigators to clarify AE reporting requirements.

5.10 Expedited Reporting of Related and Unexpected SAEs to the Research Ethics Committee

5.10.1 ACCORD is responsible for reporting SAEs that are considered to be "possibly related" and "unexpected" to the Research Ethics Committee (REC) within 15 days of becoming aware of the event.

5.10.2 Related and unexpected SAEs from double-blinded studies will be unblinded before reporting to the REC.

5.10.3 Related and unexpected SAEs reported for participants not receiving the study intervention WILL NOT be reported to the REC.

The study team WILL NOT be informed of the unblinding result.

5.10.4 In order to maintain the blind, the study team will be informed that procedures were followed and results reported where necessary to the REC.

5.10.5 Related and unexpected SAE reports will be sent to the REC with the Health Research Authority (HRA) Safety Report Form. Any relevant follow-up information will be submitted to the REC as appropriate.

5.10.6 Line listings, unless stated in the DMC Charter, will be reported by the CI to the Data Monitoring Committee (DMC) and/or the Trial Management Group (TMG) and/or the Trial Steering Committee (TSC) as appropriate.

5.10.7 In multicentre research studies, it is also the responsibility of the CI to inform the PI's at each site of all SAEs reported.

5.11 Urgent Safety Measures

5.11.1 If a safety issue is identified during a clinical trial, investigators must act immediately to protect participants from any immediate threat to their health and safety. Investigators may implement a deviation from or change to the protocol to eliminate an immediate hazard to trial participants without prior approval from the REC. This is defined as an urgent safety measure (USM).

5.11.2 The Investigator must then notify the REC and ACCORD, in writing, within 3 days of the incident. Written notification is in the form of a substantial amendment to the REC and ACCORD.

5.11.3 Notification of a USM should be delivered by;

- Emailing ACCORD at safety@accord.scot or faxing +44 (0)131 242 9447 marked urgent safety measure; and

- Sending an email or fax to the relevant main REC, marked urgent safety measure; and
- Sending an email to the relevant NHS R&D offices, marked urgent safety measure.

5.11.4 A copy of the notification and receipt must be filed in the ISF and in the TMF, if applicable.

5.11.5 Form CR010-F01 (Protocol Violation Reporting Form) will be completed by the Investigator and "urgent safety measure" will be indicated in accordance with SOP CR010 (Management of Protocol Deviations and Violations) and emailed to QA@accord.scot or faxed to ACCORD at +44 (0)131 242 9447. The QA Manager, or designee, will ensure the information is forwarded to the sponsor's representative to assess if the risk/benefit balance of the study has been altered and if it is appropriate for NHSL/UoE to continue as the sponsor.

6 REFERENCES AND RELATED DOCUMENTS

- ICH-GCP E6 Guidelines.
- CR006-T01 Serious Adverse Event Report Form (non-CTIMP)
- CR006-T02 Adverse Event Flowchart – Reporting
- CR006-T03 Non-CTIMP AE Log
- CR006-T04 Non-CTIMP SAE Follow-Up Sign Off Sheet
- CR006-F01 Cover Sheet and Return Receipt
- PV001 Pharmacovigilance: Receipt, Onward Reporting and Follow-Up of Safety Reports

7 DOCUMENT HISTORY

Version Number	Effective Date	Reason for Change
1.0	22/Mar/2011	Clarification and reporting updates
3.0	20/Feb/2014	Update for consistency with new internal procedures
4.0	13 MAR 2017	Amended procedures to align with ACCORD internal procedures associated with PV001. SOP now captures procedures for the assessment of AEs in PI absences and the reporting of USMs. ACCORD contact details have been updated throughout the SOP. Updated all associated forms and templates. Additional creation of CR006-T03 Non-CTIMP AE log.

5.0	21 MAR 2018	Addition of CR006-T04 Non-CTIMP SAE Follow-Up Sign Off Sheet. CR006-T01 Serious Adverse Event Report Form (non-CTIMP) updated.

8 APPROVALS

Sign	Date
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