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

DOCUMENT NO.:	**CR005 v5.0**
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ISSUE DATE:	**07 MAR 2018**
EFFECTIVE DATE:	**21 MAR 2018**

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 The World Health Organisation defines pharmacovigilance (PhV) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."

1.3 Adverse Event (AE) and other safety event identification, recording and reporting procedures will comply with the requirements of the Medicines for Human Use (Clinical Trial) Regulations 2004/1031 as amended and Good Clinical Practice (GCP).

1.4 Where NHSL and/or UoE agree to co-sponsor a Clinical Trial of Investigational Medicinal Product (CTIMP) with another organisation the responsibility for PhV 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, urgent safety measures (USMs) and other safety events occurring in CTIMPs that are sponsored by NHSL and/or the UoE.

3 SCOPE

3.1 This SOP applies to clinical researchers participating in CTIMPs sponsored by NHS Lothian and/or UoE. This SOP is also applicable to ACCORD members of staff responsible for PhV following ACCORD SOP PV001.

4 RESPONSIBILITIES

4.1 ACCORD will be responsible for PhV for CTIMPs that are sponsored by NHSL Lothian and/or UoE. This responsibility may not be delegated to the Investigator.

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

5 PROCEDURE

5.1 5.1 Definitions

5.1.1 Adverse Event (AE)

Any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with an Investigational Medicinal Product (IMP).

5.1.2 Adverse Reaction (AR)

Any untoward and unintended response to an IMP which is related to any dose administered to that participant.

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

Any AE or AR that at any dose:

- results in death of the clinical trial 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.

5.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Event (SUSAR) is any AR that is classified as serious (5.1.3), is suspected to be caused by the IMP and is not consistent with the IMP information in the Summary of Product Characteristics (SPC) or Investigator's Brochure (IB).

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 clinical 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 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 forms (CR005-T01 (SAE Report Form or CR005-T04 (Parent-Child (SAE) Form). Investigators will record all AEs in the AE log (CR005-T05), 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 trial, unless otherwise defined in the protocol.

5.2.5 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 trial specific procedures.

5.2.6 Template CR005-T03 (Adverse Events Flowchart - Identifying) can be used by investigators to aid AE identification and classification.

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 trial participant was taking the IMP.

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 IMP according to the following definitions:

- Unrelated: where an event is not considered to be related to the IMP.
- 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 drug.

5.5.2 In studies using a Non Investigational Medicinal Product (NIMP), the Investigator must also consider whether the AE might be linked to either the IMP or the NIMP, or whether the AE is likely to be related to an interaction between the IMP and the NIMP, even if it cannot be clearly attributed to either one of these.

5.5.3 Any AE that is considered to be related to the IMP or the NIMP or to an interaction between the IMP and NIMP, even if it cannot be clearly attributed to either one of these, is described as an Adverse Reaction (AR).

5.5.4 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 IMP, the Investigator will make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented in the IB or SPC. The event will be classed as either:

- Expected: the reaction is consistent with the toxicity of the study drug listed in the SPC or IB.
- Unexpected: the reaction is not consistent with the toxicity listed in the SPC or IB*.

*For consistency of assessing expectedness the same version of the reference safety information (RSI) in the SPC or IB should be used throughout a DSUR reporting period. However for the assessment of a Suspected Unexpected Serious Adverse Reaction (SUSAR) the most recent version of the RSI should be used to confirm the event in question is a SUSAR.

5.6.2 An AR may be described as 'unexpected' if it has occurred with greater severity than documented in the SPC or IB.

5.6.3 Any SAR that is considered to be unexpected is described as a SUSAR.

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 trial 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 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.

5.7.3 Parent-Child information

5.7.4 Events where a foetus/neonate/child suffers an SAE as a result of a medication taken by the parent then a parent-child report should be completed (CR005-T04).

5.7.5 In these instances the foetus/neonate/child is classified as the patient and all sections of the parent-child report should describe the SAE as it applies the child rather than the parent. A separate report for the parent should be generated only if the parent also suffers an SAE.

5.7.6 SAE, SAR and SUSAR reports must be as complete as possible at the time of initial reporting to ACCORD.

5.7.7 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 5.8 for reporting and 5.13 for details regarding follow-up.

5.7.8 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.

5.7.9 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.

5.8 Reporting SAEs/SARs/SUSARs to the Sponsor (ACCORD)

5.8.1 Any AE that is assessed as an SAE, SAR or SUSAR is subject to expedited reporting requirements.

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, SAR and SUSAR 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 CR005-T01 (SAE Report Form (CTIMP)) or template report CR005-T04 (Parent-Child (SAE) Form (CTIMP)) and the Cover Sheet and Return Receipt (CR005-F01). Reports will be complete as far as possible and will be signed and dated by the Investigator.

5.8.4 SAE, SAR and SUSAR 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 (CR005-F01) or send an email to confirm receipt of the SAE, SAR or SUSAR 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, SAR or SUSAR 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, SAR and SUSAR 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 Trial Master File (TMF). See also 5.13 for further details regarding follow-up.

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

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

Template CR005-T02 (Adverse Event Flowchart - Reporting) illustrates the reporting procedure and can be used by investigators to clarify AE reporting requirements.

5.9 Expedited Reporting of SUSARs to the Research Ethics Committee and the Competent Authority

5.9.1 ACCORD is responsible for reporting SUSARs to the Research Ethics Committee (REC) and Competent Authority(ies) (CA). SUSARs include events possibly related to:

- IMP
- NIMP
- Interaction between IMP and NIMP

5.9.2 Fatal or life threatening SUSARs will be reported within 7 calendar days after ACCORD is first aware of the reaction. All other SUSARs will be reported within 15 calendar days after ACCORD is first aware of the reaction.

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

5.9.4 SUSARs reported for participants receiving placebo WILL NOT be reported to the REC and CA.

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

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

5.9.6 SUSAR reports will be sent to the UK CA electronically via their electronic SUSAR website https://esusar.mhra.gov.uk/

5.9.7 SUSAR 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 and UK CA as appropriate.

5.9.8 In multicentre studies, ACCORD will inform other sites that a 'potential' SUSAR has been reported to the Sponsor. The Research Governance Manager, or designee, will inform all sites on a study that a SUSAR has been reported for that study. If the study is being coordinated by a unit/group/individual, responsibility for informing all sites of a SUSAR may be delegated to them. A basic description of the event will be provided, but the sites will remain blinded.

5.10 Urgent Safety Measures

5.10.1 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 and the UK CA. This is defined as an USM and the investigator must contact the Clinical Trial Unit at the UK CA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

5.10.2 The Investigator must then notify the UK CA in writing within 3 days of the incident. Notification is usually by email (clintrialhelpline@mhra.gsi.gov.uk) however the UK CA will advise how to notify them when first discussing the USM. Written notification in the form of a substantial amendment is also required and must be submitted to the UK CA, the REC and ACCORD. During a period in which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health, notification must be provided to the UK CA, main REC and ACCORD as soon as possible.

5.10.3 Notification of a USM should be delivered by;

- Sending an email to clintrialhelpline@mhra.gsi.gov.uk marked urgent safety measure; and
- 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.

5.10.4 A copy of the notification and receipt must be filed in the ISF and in the TMF or Sponsor File.

5.10.5 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.

5.11 Expedited Reporting of Other Events

5.11.1 The following safety issues will also be reported to ACCORD in an expedited fashion, using the same methods (as described in section 5.8).

1. An increase in the rate of occurrence or a qualitative change of expected SAR, which is judged to be clinically important.
2. Post-study SUSARs that occur after the trial participant has completed a clinical trial and are notified by the investigator to the sponsor.
3. New events related to the trial or the development of the IMPs and likely to affect the safety of the participants.
4. Recommendations of the DMC where relevant for the safety of the trial participants.
5. Any reaction due to a NIMP that is likely to affect the safety of trial participants.

5.11.2 The Research Governance Manager, or designee, is responsible for informing the main REC and UK CA of these safety issues within the same

timelines as described in section 5.9. A copy of the letter and any follow-up information and correspondence will be kept in the TMF or Sponsor File.

5.12 Pregnancy Reporting

5.12.1 Pregnancy is not considered to be an AE or SAE, however the Investigator must collect pregnancy information for any female study participants or female partners of male study participants who become pregnant while participating in a study.

5.12.2 Any pregnancy that occurs in a trial participant or their partner during a study should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery in accordance with the study protocol.

5.12.3 The Investigator will record the information on Form CR005-F02 (Pregnancy Notification Form) and send this to ACCORD (details found in section 5.9) office within 14 days of being made aware of the pregnancy.

5.13 Follow-Up

5.13.1 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).

5.13.2 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)
- Death (including date of death).

5.13.3 In the case of parent-child reports where the seriousness criteria has been assessed as “Congenital anomaly/birth defect”, the Investigator must follow-up with the child and provide the sponsor with any relevant updated information until the trial has ended.

5.13.4 All new information/follow-up information must be initialled and dated on the follow-up reports.

5.13.5 Follow-up reports should be submitted to the sponsor (ACCORD) as per section 5.8. If required, the CTIMP SAE Follow-Up Sign Off Sheet (CR005-T06) should be completed alongside the original SAE form.

5.14 External Contracting of SAE, SAR and SUSAR Reporting

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

5.15 Requests for SAE Line Listings

5.15.1 Requests for SAE line listings for specific trials can be made by the trial team (e.g. CI, Trial Manager, statistician) to the ACCORD office via resgov@accord.scot.

5.15.2 A minimum of 2 weeks notice should be given by the requestor to ACCORD for the generation of a trial-specific line listing.

5.15.3 The request should detail the trial name and the reporting period required.

5.16 Data Monitoring Committee Meetings

5.16.1 Line listings, unless stated in the Data Monitoring Committee (DMC) Charter, will be reported by the CI, or designee, to the DMC and/or the Trial Management Group (TMG) and/or the Trial Steering Committee (TSC) as appropriate. Listings may be requested for this purpose as detailed in 5.15.

5.16.2 The trial team will provide ACCORD with a copy of the DMC meeting minutes/recommendations so the Sponsor is aware of any issues raised by the DMC.

6 REFERENCES AND RELATED DOCUMENTS

- The Medicines for Human Use (Clinical Trials) Regulations, (SI 2004 No. 1031) as amended
- European Commission Guidance Document 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicine products for human use', April 2006
- National Institute for Health Research Clinical Trials Toolkit, 2012
- European Commission Guidance Document 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials' (Volume 10, Clinical Trials), May 2007
- CR005-T01 SAE / SAR / SUSAR report
- CR005-T02 Adverse Event Flowchart – Reporting
- CR005-T03 Adverse Event Flowchart – Identifying
- CR005-T04 Parent-Child SAE report

- CR005-T05 CTIMP Adverse Event Log
- CR005-T06 CTIMP SAE Follow-Up Sign Off Sheet
- CR005-F01 Cover Sheet and Return Receipt
- CR005-F02 Pregnancy Notification Form
- CR010 Management of Protocol Deviations and Violations
- 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	N/A
2.0	14 SEPT 2011	Amend reporting forms and clarify procedures
3.0	20 FEB 2014	Amended procedure to follow ACCORD internal procedures, modified fax cover sheet and reporting forms
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 which version of the RSI to use when assessing SUSARs. Updated information regarding the reporting of USMs added. ACCORD contact details have been updated throughout the SOP. Updated all associated forms and templates. CR005-W01 made obsolete. Relocation of the AE Log (CR005-T05) from CR007 to CR005.
5.0	21 MAR 2018	Addition of CR005-T06 CTIMP SAE Follow-Up Sign Off Sheet. CR005-T01 updated.

8 APPROVALS

Sign	Date
SIGNATURE KEPT ON FILE AUTHOR: Raymond French, Clinical Research Governance Manager, UoE, ACCORD	
SIGNATURE KEPT ON FILE APPROVED: Heather Charles, Head of Research Governance, NHSL, ACCORD	
SIGNATURE KEPT ON FILE AUTHORISED: Lorn Mackenzie, QA Manager, NHSL, ACCORD	