STANDARD OPERATING PROCEDURE

Adverse Events and Safety Reporting

CG-QMS SOP CG10

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Approved by: Signature:	UREC See original

Version History	**Reason for change**

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED

1. PURPOSE

To outline the necessary procedures for reporting adverse events and serious adverse events for clinical trials sponsored by the University of Lincoln or supported by the Lincoln Clinical Trials Unit (LinCTU).

2. SCOPE

This SOP applies to all UoL sponsored clinical research or where LinCTU are providing support in Trial Management.

3. BACKGROUND

3.1 The Medicines for Human Use (Clinical Trials) Regulations (2004) as amended, interpret an adverse event to be "any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product".

3.2 An Adverse Events (AE) means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to the trial intervention.

3.3 An Adverse Reaction (AR) means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

3.4 A Serious Adverse Events (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

3.5 Means an adverse event, adverse reaction or suspected unexpected adverse reaction respectively that

a) results in death

b) is life threatening

c) requires hospitalisation or prolongation of existing hospitalisation

d) results in persistent or significant disability or incapacity or

e) consists of a congenital anomaly or birth defect

f) anything the Investigator deems to be of Clinical significance

3.6 The Medicines for Human Use (Clinical Trials) Regulations (2004) as amended state that an unexpected adverse reaction is "unexpected" if its nature and severity are not consistent with the information about the medicinal product.

a) "In the case of a product with a marketing authorisation, in the summary of the products characteristics for that product."

b) "In the case of any other investigational medicinal product, in the investigational brochure relating to the trial in question."

3.7 Therefore, a SUSAR is an

- Assessment - Assessment of event
- Causality - Possible related or related
- Seriousness - Classified as a Serious Adverse Reaction, yet it becomes a SUSAR as it is...
- Expectedness - Unexpected

3.8 All adverse reactions that are suspected to be related to an investigational medicine product that are both serious and unexpected are considered to be SUSAR's.

3.9 The Chief Investigator (CI) has overall responsibility for the reporting of any adverse events, as detailed above, to the relevant competent authorities and sponsor within the set timelines. However, day-to-day reporting may be delegated to a person with the relevant knowledge, skills and experience and experience as recorded on RF CG08-RF01 Study Delegation Log.

3.10 The local Principal Investigator (PI) for multi-site trial has overall responsibility for the reporting of any adverse events, as detailed above, to the relevant competent authorities and sponsor within the set

timelines. However, day-to-day reporting may be delegated to a person with the relevant knowledge, skills and experience and experience as recorded on RF CG08-RF01 Study Delegation Log.

a. Note The local Principal Investigator must ensure that appropriate procedures are in place locally to provide assurance that SAEs are recognised, and that staff are appropriately trained to fulfil the reporting requirements.

Urgent safety measures (all studies)

3.11 A sponsor or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

3.12 The main Research Ethics Committee (REC) (and the MHRA for CTIMPs) must be notified immediately and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

Safety reporting for clinical trials of investigational medicinal products (CTIMPs)

3.13 The following must be reported to the MHRA:

- Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Development Safety Update Reports (DSURs)
- Any significant findings and recommendations of an independent data monitoring committee or equivalent body established for the trial.

Safety reporting for non-CTIMP studies

3.14 For all other studies, including clinical investigations of medical devices, the approved Research Ethics Committee (REC) should be notified only of reports Serious Adverse Events (SAEs) that are:

- related to the study (i.e. they resulted from administration of any of the research procedures) and
- unexpected (i.e. not listed in the protocol as an expected occurrence)

3.15 The trial protocol should outline adverse events and any reporting requirements, including unblinding for blinded trials.

4. CROSS REFERENCES

4.1 ICH GCP

4.2 Clinical Trial Regulations - SI 2004/1031 The Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments

4.3 eSUSAR website https://esusar.mhra.gov.uk

4.4 Trial Protocol

4.5 CG-QMS CG09-RF01 Screening and Enrolment Log

4.6 CG-QMS RF CG08-RF01 Study Delegation Log

4.7 CG-QMS RF CG10-RF01 SAE Report Form

5. PROCEDURE

5.1 Individual adverse events should be assessed (using Appendix 1 as a guide) by the Investigator or a delegated member of the team and reported as specified in the protocol, ideally within 24 hours.

5.2 All AEs must be documented clearly, including any explanation of the patient's definition of the event.

5.3 An SAE may be notified verbally in the first instance to discuss the event and determine any urgent safety or emergency procedures.

4.8 An SAE should be documented using RF CG10-RF01 SAE Report Form, reporting and notification should be in accordance with the Protocol or this SOP.

5.4 The SAE Report Form must be signed by the CI, PI or designated nominee. Where the SAE is not at the CIs site, a copy of the completed Report Form should be emailed to the CI / LinCTU.

5.5 The Chief Investigator, Principal Investigator and LinCTU (as necessary) should be notified within 24 hours of event onset or of the event being assessed as serious.

Clinical Trials of IMPs (CTIMPs)

5.6 In the event of an SAE being classified as a SUSAR, the Chief Investigator or designated nominee must:

5.7 Notify the MHRA via the eSUSAR website https://esusar.mhra.gov.uk[1]

a. Fatal or life-threatening SUSARs must be reported as soon as possible, but **no later than 7 days** being made first aware of the reaction. Any additional relevant information must be sent **within 8 days** of the report.

b. Non-fatal or non-life threatening SUSARs must be reported as soon as possible but **no later than 15 days** after you are first aware of the reaction.

5.8 Inform the sponsor, download a copy of the eSUSAR report and send via email. The sponsor should be kept informed at all times.

5.9 Inform the REC that approved the study. Provide a copy of the eSUSAR report along with a completed CTIMPs Safety Report form. The REC will process the report in accordance with Safety and progress reports (CTIMPs) procedural table.

Non-IMP Clinical Trials:

5.10 In the event of an SAE being deemed directly related to and an unexpected result of any trial treatment or procedure the Chief Investigator must:

5.11 Within 15 days inform the REC that approved the study using the Non-CTIMP safety report to REC form. The REC will process the report in accordance with Safety and progress reports (other research) procedural table.

5.12 All clinical trials

5.13 Inform the participating site in accordance with any local reporting requirements. A copy of any internal reports should also be retained in the TSF / ISF.

5.14 Inform any other trial committee or organisation that needs to be informed according to the trial protocol.

5.15 Copies of all correspondence relating to the SAE should be copied to the sponsor.

Note: Correspondence relating to Adverse Events does not need to be sent.

5.16 All decisions related to an SAE must be clearly documented including a timeline of the events and any urgent safety measures undertaken. A copy of all correspondence relating to the SAE should be stored in the TMF and ISF.

5.17 Any SAE should also be documented in the participant's NHS medical notes (where the participant is an NHS patient).

[1] 5.1 *In order to be able to access the eSUSAR website https://esusar.mhra.gov.uk you must be allocated an account by the trial Sponsor. For UoL sponsored studies please contact sponsor@lincoln.ac.uk for clinical trials sponsored by another organisation please contact the sponsor's office.

Annual Progress and Annual Safety Reports

5.18 A progress report should be submitted to the REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given.

Note: Progress Reports are only required for studies that are more than two years in duration and for Research Tissue Bank and Research Databases. There is no requirement for a Progress Report for Proportionate Review studies and where the study is two years or less in duration.

5.19 There are separate forms for submitting progress reports, depending on the type of research.

5.20 An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

Annual progress report form for clinical trials of investigational medicinal products (CTIMPs)

Annual progress report form for all other research

Annual Report form for Research Databases

Annual Report form for Research Tissue Banks

Development Safety Update Reports (DSURs) – CTIMP studies

5.21 DSURs should be submitted annually and take into account all new available safety information received during the reporting period.

5.22 The DSUR should include:

- a cover letter listing all EudraCT numbers of trials covered by the DSUR. Please include an email address for correspondence.
- an analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)
- Full details of what to include in a DSUR can be found in the ICH E2F guidance.

5.23 The DSUR should be submitted using MHRA Submissions via the Human Medicines Tile. Selecting 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list.

5.24 **Shortened DSURs** should be submitted annually and are suitable for individual trials that are authorised under the Notification Scheme which are not part of a multi-study development programme.

5.25 Phase 4 national (UK only) trials of licensed products, and where all participants have completed treatment and are only in follow-up will also be suitable for submission of a short format DSUR.

5.26 A shortened DSUR may be completed using the Health Research Authority Annual Progress Report. When submitting to the MHRA include Annual Progress Report (APR) in lieu of a full DSUR and include the EudraCT number and CTA reference number. Providing a list of all serious adverse reactions in section 6 of the APR.

5.27 A copy all of Annual Progress and Annual Safety Reports should be retained in the TMF / ISF.

5.28 Where relevant inform any other trial committee or organisation that needs to be informed according to the trial protocol.

6. FLOW CHART

Not required.

7. APPENDIX ONE

ADVERSE EVENT ASSESSMENT

Adverse events undergo three main assessments:

Assessment of Seriousness

This is based on the regulatory definitions of seriousness defined above. This definition must also be included in the trial protocol. The term 'severe' is often used to describe the intensity (clinical severity) of a specific event. This is not the same as 'serious', which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

Assessment of Causality

This is a clinical assessment of whether the adverse event is likely to be related to trial intervention. All adverse events judged as having a reasonable suspected causal relationship to the IMP are considered to be adverse reactions. The expression 'reasonable suspected causal relationship' is meant to convey in general that there is reason (e.g. facts, evidence or arguments) to suggest a causal relationship.

Many terms and scales are in use to describe the degree of certainty in relation to causality between an IMP and an event, such as certainly, definitely, probably or possibly; or likely related or not related. Whichever system is used, this should be specified and explained in the protocol, and the events that qualify as SARs should be made clear.

Assessment of Expectedness

The 'expectedness' of an adverse reaction to an IMP is assessed in the light of the Reference Safety Information (RSI) for that product which for clinical trials is contained in either:

- The summary of product characteristics (SmPC) for a product with a marketing authorisation; or
- The investigator's brochure (IB) for any other investigational medicinal product.

However, documentation of previous reports of an event in the SmPC or IB does not automatically qualify an event to be expected. For example, a particular event may be deemed more severe or occur more frequently than documented.

The Clinical Trials Regulations require that the sponsor shall ensure that the investigator's brochure is validated and updated at least annually.

Competent authority approval is required if the Reference Safety Information (RSI) (i.e. IB or SmPC) on which expectedness is judged, is modified or changed. This constitutes a substantial amendment to the CTA. However, annual updates to the investigator's brochure which do not alter the benefit-risk assessment of the trial should not be submitted as substantial amendments.

Where a trial is taking place in more than one country, using a licensed medicine with different SmPCs around the globe, a single SmPC and labelling information (the most appropriate with reference to subject safety) should be selected as the Reference Safety Information for all trial sites and this should be documented in the protocol. If the sponsor is not the Marketing Authorisation Holder for the IMP, a system to monitor whether there has been any update to the SmPC should be implemented.

The electronic Medicines Compendium (eMC) contains up to date information about medicines licensed for use in the UK.

Adapted from: MRC/DH joint project to codify good practice in publicly-funded UK clinical trials with medicines https://www.ct-toolkit.ac.uk/routemap/risk-assessment/downloads/joint-project-pharmacovigilance.pdf