Dorset HealthCare University
NHS Foundation Trust

Standard Operating Procedure for Adverse Event, Serious Adverse and Suspected Unexpected Serious Adverse Reactions Reporting

Objectives	The objective of this SOP is to explain the local processes for reporting adverse and serious adverse events, as well as suspected unexpected serious adverse reactions.
Scope	This SOP applies to all research study staff.
Responsibility	It is the responsibility of individual research study staff to adhere to this SOP.
Related Document	None.

1 Purpose

The purpose of this Standard Operating Procedure (SOP) is to explain the local process, and requirements, for reporting Adverse and Serious Adverse Events, as well as Suspected Unexpected Serious Adverse Reactions, for both multicentre studies that Dorset HealthCare (DHC) is taking part in and studies which are sponsored by DHC.

2 Introduction

ICH Good Clinical Practice guidelines require all adverse events (AE's) and serious adverse events (SAE's) experienced by a research subject to be documented and reported.

2.1 Definitions

2.1.1 Adverse Event:

Any unplanned medical occurrence after the subject has consented for the study whether or not they have received study medication is classed as an adverse event. An adverse event can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease, including, for example, a cold or an accident.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions.

The expression "reasonable causal relationship to a medicinal product" means to convey in general that there is evidence or argument to suggest a causal relationship.

2.1.2 Adverse Reaction:

Any untoward and unintended responses to an investigational medicinal product related to any dose administered.

2.1.3 Unexpected Adverse Reaction (UAR):

An adverse reaction, the nature and severity of which is not consistent with the applicable product information (e.g. investigator's brochure or summary of produce characteristics).

2.1.4 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):

Any AE, AR or UAR that at any dose:

- Results in death
- Is life-threatening
- Results in patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly / birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardise the patient or may require intervention to prevent any of the outcomes listed above may also be considered serious.

This SOP describes the procedure for eliciting, recording and reporting adverse and serious adverse events.

3 Training

New users must read and understand this SOP before carrying out this procedure. Existing users must read and understand the Revisions Section.

All users must have undergone recent GCP training.

4 Revisions

This is the second version of this SOP.

5 Procedure

At each visit or study assessment adverse events that might have occurred since the previous visit or that are occurring at that time should be elicited. Patients should also be encouraged from the outset of any study to contact the research team at the time of any adverse event where possible.

Adverse events ongoing at study completion should be followed up as per the requirements of the protocol and as clinically indicated.

5.1 Assessment of an Adverse Event

Assessment of an adverse event covers three main areas:

- **Assessment of Seriousness** – this is based on the regulatory definitions of seriousness (patient / event outcome or action criteria).

  Any AE, AR or UAR that at any dose:

  - Results in death
  - Is life-threatening
  - Results in patient hospitalisation or prolongs existing hospitalisation
  - Results in persistent or significant disability/incapacity
  - Results in a congenital anomaly / birth defect

- **Assessment of Causality** – a clinical assessment of whether the adverse event is likely to be related to the trial drug. All adverse events judged as having a reasonable suspected causal relationship (definitely, probably or possibly related) to the drug are considered to be adverse reactions. The local investigator responsible

for the patient should make the immediate assessment, distinguishing suspected adverse reactions from unrelated adverse events.

- **Assessment of Expectedness** – the evaluation of expectedness is based on knowledge of the adverse reaction and any relevant product information. The list of expected events should be based on:
    - the Summary Product Characteristics (SPC) for the products under investigation for a licenced drug; and/or
    - the Investigator's Brochure (IB) for a non-licenced drug.

5.2 Adverse Event Reporting:

When an adverse event occurs, the following must be recorded in the patient's medical record and the study Case Report Form (CRF). In addition some study protocols may require completion of study-specific adverse event reporting forms.

- Record each untoward occurrence as separate adverse events. For example, nausea and vomiting should be recorded as two adverse events.
- Document the nature of the adverse event(s) in an unambiguous way using precise and specific terminology.
- Record start and stop times and dates of the adverse event(s) as accurately as possible. Refer to the protocol for advice on estimate of dates.
- Document the severity of the adverse event(s) as guided by the study protocol (usually mild, moderate or severe).
- Document any action taken regarding the study drug or study procedures.
- Document any treatment/medication given or action taken in relation to the adverse event(s).
- Document the outcome of the adverse event(s).

5.3 Serious Adverse Event/Reaction Reporting

5.3.1 All serious adverse events/reactions will be documented as above.

5.3.2 Researchers must inform the study organising body IMMEDIATELY (within 24 hours) of becoming aware of the serious adverse event. Further details on informing the study organising body of serious adverse events and emergency contact telephone numbers will be fully detailed in the study protocol.

5.3.3 All SAEs must be reported promptly even if the outcome or specific details are not yet known. An initial SAE report should contain only the patient's details and the presumed diagnosis based on presenting symptoms. The SAE should ONLY be signed by the Principal or Sub-Investigator, and the causality and expectedness assessment must only be undertaken by these members of staff. An un-signed SAE may be submitted to avoid delay in reporting the event. Where possible, the follow-up SAE should be sent within a further 24 hours, even if full diagnosis and management plan is not yet known. It is acceptable to send the first follow-up SAE with the comment 'no further information yet available' or 'results not back from laboratory/radiology'. A fully-completed and PI-signed report must be sent at the earliest opportunity.

5.3.4 Requests from the study organising body for further information of the serious adverse event must be promptly responded to.

5.3.5 Reporting SAEs over a weekend – In accordance with GCP, the research must notify the sponsor of an SAE as soon as they are aware of the event. If the Investigator is on call and in the hospital over the weekend, they must report it straight away. In the same manner,

should the research nurse/data manager be informed that a patient is admitted over the weekend (should they be working) they must report the SAE.

5.3.6 Otherwise the research nurse/researcher would be alerted to the SAE event when they are next in work, and would report the event immediately. This is the same for SAEs in the evening. If you are aware of the admission late in the working day, you must complete the initial report prior to leaving for the day.

5.4 Guidance on Pregnancy Follow-up

5.4.1 Any pregnancy that occurs during trial IMP administration, whilst not an adverse event, requires monitoring and follow-up to term. Pregnancies and outcome will be included in signal detection (when there are several reports of adverse reactions to a particular drug this process may lead to the detection of a signal – an alert about a possible hazard communicated to members countries. This happens only after detailed evaluation and expert review) and annual safety reports.

5.4.2 The Chief Investigator will report any pregnancy occurring on a clinical trial via the SAE report form to the study organising body in the manner described above. Each pregnancy will be followed up until the outcome of the pregnancy is known. The Chief Investigator will liaise with the relevant Obstetrician throughout the pregnancy.

5.4.3 A database record of all pregnancies will be held by the study organising body, this will include follow-up to term and where appropriate, long term follow-up of the baby may be required.

5.5 Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting:

5.5.1 The MHRA now have an electronic reporting site for SUSARs.

5.5.2 In the case of DHC Sponsoring a CTIMP: The Chief Investigator, the Research Manager / named person from the research team, R&D and Sponsor representative must all have an eSUSAR account.

To register please use the following web addresses:

https://esusar.mhra.gov.uk/

https://esusar.mhra.gov.uk/about/

5.5.3 If an SAE is deemed to be a SUSAR, a Ulysses incident form must be completed and submitted according to the DHC procedure for risk reporting (for both 'participating site' and 'Co-ordinating site' status). N.B. SUSARs must be reported to the MHRA blinded (only unblinding in an emergency).

5.6 Development Safety Update Report (DSUR) – the revised format for the Annual Safety Report (ASR)

5.6.1 In addition to the expedited reporting required for SUSAR, Sponsors are required to submit a DSUR to the MHRA and the Ethics Committee once a year throughout the clinical trial or on request. The development safety update report should take into account all new available safety information received during the reporting period.

5.6.2 The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by: (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety; (2) describing new safety issues that could have an impact on the protection of clinical trial subjects; (3) summarising the current understanding and management of identified and potential risks; and (4) providing an update on the status of the clinical investigation/development programme and study results.

5.6.3 A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

5.6.4 In the event of more than one sponsored or co-sponsored trial involving the same IMP, the Sponsor or Co-Sponsor via the Research & Development Facilitator will liaise with the CI's involved to produce only one report for all concerned trials.

5.6.5 DSUR Data Lock Point – The "Development International Birth Date" (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide. The data lock point of the DSUR should be last day of the one-year reporting period.

5.6.6 The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR Data lock point.

5.6.7 The aim of the DSUR is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety of subjects included in these studies.

5.6.8 Full details of what to include in a DSUR can be found using this website link:

http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

https://www.fda.gov/downloads/drugs/guidances/ucm073109.pdf

5.6.9 You must submit your DSUR using CESP http://cesp.hma.eu/Home. The same guidance for submitting clinical trials applications via CESP applies, but please select regulatory activity G0042 - Development Safety Update Reports.

6 Appendices

There are no appendices to this SOP.

7 Responsibilities

All staff in contact with trial subjects are responsible for noting adverse events.

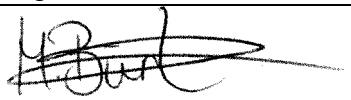
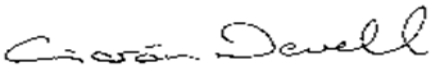
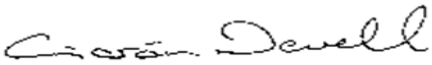
It is the responsibility of the Principal Investigator at local research sites to ensure that these reporting requirements are met at their site.

Chief Investigators must prepare and disseminate a written report of all serious adverse events to local research sites. Copies of this report are to be filed in the study file.

8 Review

This SOP should be reviewed every two years unless new guidance or legislation dictates a review any sooner.

Date reviewed: 12/04/2019 Date of next review: 12/04/2021

Written By	Signature	Date
Hazel Burt		12/04/19
Reviewed By	Signature	Date
Dr Ciarán Newell		12/04/19
Authorised By	Signature	Date
Dr Ciarán Newell		12/04/19