PV Office Processing for Clinical Trials of Investigational Medicinal Products

1. Introduction

This guideline outlines the process to be followed when a Serious Adverse Event (SAE) report for a Clinical Trial of Investigational Medicinal Products (CTIMP) is submitted to the Pharmacovigilance (PV) Office for sponsored trials.

All SAEs in a CTIMP must be reported to the Sponsor within 24 hours of awareness of the event, unless otherwise specified in the Safety Reporting Plan (Form 55.001A).

The Safety Reporting Plan should always be consulted when processing SAE reports as other study-specific arrangements may be in place.

2. PV Office Trial Set-up

Following formal notification by the PV and Safety Manager, the PV Office will create a study folder in the relevant area of the filestore held at the Robertson Centre for Biostatistics (RCB)

The filestore folder should be named according to the following format:
ShortName_EudraCTNo_SponsorNo_CI Surname

3. SAE Receipt

Initial and follow-up SAE reports can be submitted to the PV Office as follows:

- On a paper SAE form (generic or study-specific) by fax or email
- Verbal report by telephone
- Using reporting procedures built into a study GCTU eCRF application

3.1 Paper reports:

a. Completed paper SAE report forms will be emailed to the PV Office or faxed directly to the PV Office fax number (which triggers an automatic email alert to be sent to PV Office personnel)
b. The handwritten report will be saved and reviewed by the PV Office following the processes detailed in sections 4 and 5
c. The PV Office will acknowledge receipt of the paper report by email. The acknowledgement email will include any queries resulting from the initial review by the PV Office and will be saved within the SAE folder as detailed in section 4
d. With regards to trials that use eCRF reporting procedures, the site staff responsible for submitting the report will be instructed to complete an SAE report via the trial eCRF

3.2 Verbal reports:

a. Any call received at the GCTU requesting to report a SAE will be directed to the PV Office. Should PV personnel be unavailable, the call should be directed to the PV and Safety Manager or a member of RCB Senior Management
b. The reporter will be asked to provide as much information about the SAE as possible, with a minimum of the following details:
    - Reporter (name, site, email address, phone number)
    - Study (study name, EudraCT number or other reference number, if available)
    - Participant ID
    - Diagnosis

- Seriousness criteria
- Causality and expectedness (if applicable)

c. The PV Office will acknowledge receipt of the verbal report by email. This email will detail the information provided verbally and will be saved within the SAE folder as detailed in section 4
d. With regards to trials that use eCRF reporting procedures, the site staff responsible for submitting the report will be instructed to submit the SAE information to the eCRF within 48 hours of submitting the verbal report. For all other trials, the reporter will be instructed to follow up the verbal report with a paper report within 48 hours of the verbal report

3.3 eCRF reports:

a. Where studies have reporting facilities built into an eCRF application, an automatic email alert will be triggered upon input of an SAE report by site staff. This alert is sent to the PV Office and relevant Sponsor and study personnel. The PV Office will save copies of the automatically generated emails in a chronological order, ensuring that the Report No is added to the file name to allow for easy identification
b. The PV Office will download a copy of the .pdf report from the eCRF application. This will be saved and reviewed by the PV Office following the processes detailed in sections 4 and 5

4. Tracking and Storage

All SAE reports and related SAE correspondence will be saved electronically in the relevant filestore folders.

For each parent SAE, a folder will be created as a sub-folder to the applicable participant number.

SAE reports will be saved as .pdf files and in a consistent format for each trial. At a minimum this must include the participant number and report number.

On receipt of an SAE report, a member of the PV Office will create an entry on the relevant SAE tracker spreadsheet. This entry will be attributed to the PV Office personnel handling the SAE and will be updated as and when additional information is provided.

5. PV Office SAE Review

5.1 Initial SAE Reports

PV Office personnel will perform the following checks on receipt of an initial SAE report:

a. If a paper report is received, are the trial and subject identifiers included on every page? If not, PV Office staff will contact the site and ask for the missing details to be added and a new copy sent through
b. Has the SAE been reported within 24 hours of the site becoming aware of the event? If not, PV Office personnel will remind the site of the need to report SAEs within 24 hours of awareness
c. Is there a diagnosis? If there is no text provided in the diagnosis field, or if the text indicates that the event is unknown or unconfirmed, this should be queried with site staff until resolution. Should any of the text require further review (i.e. the event appears to be complex, or does not appear to be consistent), the PV and Safety Manager (or Sponsor delegate) should be contacted
d. Has a narrative been provided and are any dates included consistent with date fields elsewhere on the report?

e. Has the seriousness criteria been assigned and is this consistent with the narrative?
f. Does the SAE have an outcome that is consistent with the seriousness criteria and narrative?

Should any of the above items be missing or inconsistent, the PV Office should query the information with the site personnel responsible for submitting the SAE and/or notify the PV and Safety Manager, as required.

5.2 Initial Review of Causality and Expectedness

PV Office personnel will perform the following actions to ensure that the SAE is reviewed as per the regulatory requirements.

For all trials, causality **must** be provided by a local investigator, be it the Principal Investigator (PI) or another delegated investigator.

Assessment of expectedness differs between trials and so the Safety Reporting Plan should be consulted to identify the party responsible for this review. However; for all trials the CI or Sponsor PV manager can assign expectedness

For trials where the PI/local investigator is responsible for assessment of causality and expectedness within the protocol, the following steps should be followed:

a) Check for an assessment of causality and expectedness by a local investigator at the site (PI or another clinician with relevant permissions). If this review has not been completed, this should be queried with the reporting site by the PV Office
b) Where an SAE has been assessed as related by the local investigator, the PV and Safety Manager should be notified of the event
c) The CI or PV and Safety Manger may assess expectedness where required

For trials where the PI/local investigator is responsible for the assessment of causality but the Chief Investigator (CI)/Sponsor are responsible for the review of expectedness, the following steps should be followed:

a) Check for an assessment of causality by a local investigator at the site (PI or another clinician with relevant permissions). If this review has not been completed, this should be queried with the reporting site by the PV Office
b) Where an SAE has been assessed as related by the local investigator, the CI (or delegated clinician) should be notified of an event that requires their assessment of expectedness
c) In the event that the CI (or delegated clinician) does not review the SAE within 5 days (fatal or life-threatening events) or 10 days (all other events) from the date of Sponsor awareness, the PV and Safety Manager should be notified of an event that requires them to assess expectedness

Although the assessment of causality and expectedness should primarily be via the trial eCRF there may be circumstances where this is not possible, expediency is required, or where appropriate personnel cannot access the eCRF. In such cases relevant personnel may carry out their assessment of causality and expectedness by email or, if required, via telephone. Where this occurs, the email or record of telephone report should be filed in the filestore alongside the relevant SAE. In such cases the person carrying out the assessment should also be reminded that they must also complete their assessment via the eCRF.

5.3 PV and Safety Manager

The PV and Safety Manager is responsible for:

a. For all events assigned as related, reviewing and confirming the expectedness assessment against the approved Reference Safety Information (RSI). Any inconsistencies should be raised with the investigator carrying out the assessment of expectedness. Should the PV and Safety Manager be unable to assess expectedness within to the required timelines (e.g. due to holiday or absence), the PV Office will contact the CI (or their delegate) to review and confirm the expectedness assessment of any related events unless the CI has already carried out the assessment of expectedness
b. Reviewing SAEs escalated by the PV administrators for clinical consistency and data discrepancies, including whether the SAE contains multiple events which require splitting
c. Reviewing SAEs escalated by the PV administrators to ensure that they meet protocol defined reporting requirements
d. Where an event is assigned as related to the IMP and unexpected as per the RSI (i.e. potential SUSAR), the PV and Safety Manager should discuss this with the reporting investigator. In all cases, should the event be classified as a SUSAR following these discussions, it should be reported to the MHRA and REC

5.4 CI (or Clinical Delegate)

The CI (or their clinical delegate) is responsible for:

a) Assignment of expectedness for related SAEs in line with the protocol and Safety Reporting Plan
b) Providing a second opinion of causality where requested or where this is a requirement specified within the Safety Reporting Plan and trial protocol
c) Review of all SUSARs prior to submission to the MHRA and REC

5.5 Follow-up SAE Reports

Upon receipt of a follow-up report for an SAE, the following checks should be made:

For events assessed by the local investigator as related:

a. Has there been a change in the seriousness criteria or outcome to indicate that a previously non-life threatening/non-fatal event is now considered to be life threatening or fatal?
b. Has there been a change in the assessment of causality from related to unrelated by the local investigator?
c. Have new event terms been added or has the event term changed significantly?

Should any of the above conditions be met, the follow-up report will require the expectedness of the event to be reassessed as per section 5.2. The SAE should be processed according to section 5.1 and within the timelines set out in section 6.

For events assessed by the local investigator as unrelated:

a. Has the assessment of causality changed from unrelated to related?

Should the above condition be met, the follow-up report will require reassessment of causality and expectedness as per section 5.2 and should be processed as per section 5.1 within the timelines set out in section 6.

6. PV Office Timelines for PI/CI Review

The regulatory timelines for SUSAR reporting are: 7 days for fatal or life-threatening SAEs or 15 days for all other SAE outcomes. To enable the PV Office to meet the regulatory requirements, this 7/15 day timeframe is directly translated into the maximum timeframe for review and sign-off of SAEs.

SAEs should be reviewed by the relevant personnel, as per section 5.2, within 5 or 10 days respectively. This allows sufficient time for any discussion that may be required regarding the causality and expectedness of the event, and for submission to the MHRA should the event meet SUSAR criteria. For trials considered high risk, earlier review may be required, and this will be detailed in the Safety Reporting Plan.

All other incidental information can be submitted by the site without risk of exceeding the timelines required for clinical review and sign-off; however, the PV Office will still query missing items as defined in section 5.

7. Downgrading of an SAE report

If a follow-up report identifies that a previously reported event is no longer considered by the PI to be an SAE, the report will not be removed from filestore, but it will be identified as "NOT AN SAE" by adding a suffix to the folder name. The corresponding entry will also be removed from the study tracker.

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Document History

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