

Standard Operating Procedure CCTU/SOP002

Pharmacovigilance Process for Investigator Teams

1. Scope

The Trust as Sponsor delegates the responsibility for pharmacovigilance to the Chief Investigator of the Clinical Trial of an Investigational Medicinal Product (CTIMP).

2. Purpose

To provide an explicit guide on the responsibilities delegated to the Chief Investigators by the Sponsor regarding Pharmacovigilance. The Sponsor is required under the Clinical trials Regulations to ensure that adverse events are appropriately recorded, reviewed, and reported to the Research Ethics Committee (REC) and the Medicines and Healthcare Products Regulatory Agency (MHRA).

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

Common abbreviations and definitions can be found in CCTU/INF001 Common Abbreviations and Definitions.

3.1. Definitions

Term	Definition
Trust-Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH) or sponsored by CUH jointly with The University of Cambridge
eSUSAR	Electronic reporting of SUSAR's
Adverse Event (AE)	Any untoward medical occurrence that happens to a patient or research participant to whom investigational medicinal product has been administered in a clinical trial, which may or may not necessarily have causal relationship with the research being undertaken.
Adverse Reaction (AR)	An untoward and unintended reaction that is considered to be related to the administration of the IMP.
Serious Adverse Event (SAE)	Any AE or effect that at any dose: <ul style="list-style-type: none">• Results in death• Is life threatening• Requires hospitalisation or prolongation of existing

	<p>hospitalisation</p> <ul style="list-style-type: none"> • Results in persistent or significant disability/incapacity • Is a congenital anomaly/birth defect • Is an otherwise significant event
Serious Adverse Reaction (SAR)	An SAE that is considered to be possibly, probably or definitely related to the IMP.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction, which is both serious and unexpected, i.e. the nature or severity of which is not consistent with the applicable product information and which fulfils one or more of the criteria listed above for SAE.
Pharmacovigilance	Pharmacovigilance is the ongoing monitoring of the safety profile, combined with the ongoing assessment and evaluation of the risk-benefit of medicines. This process is important to identify adverse reactions, identify previously unrecognised adverse reactions and changes in patterns of known adverse reactions. Pharmacovigilance is the key activity to prevent harm to the trial subject and patients by ensuring that medicines put onto the market are safe.

3.2. Abbreviations

Abbreviation	Meaning
CUH	Cambridge University Hospitals NHS Foundation Trust
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
DSUR	Developmental Safety Update Report
MHRA	Medicines and Healthcare Products Regulatory Agency
REC	Research Ethics Committee
IMP	Investigational Medicinal Product

4. Undertaken by

This SOP applies to Chief/Principal Investigators and their trial teams involved in the management of Trust-sponsored CTIMPs.

5. Items Required

CCTU/FRM001 SAE/ SAR Reporting Form
 CCTU/FRM006 AE Recording Log
 CCTU/FRM003 Pregnancy Reporting Form
 CCTU/GD003 eSUSAR Reporting Investigators Guide
 CCTU/FRM004 Other Important Safety Issues
 CCTU/FRM002 SAE Query Form

6. Summary of Significant Changes

Addition of SAE Querying guidance
Revision of ASR section to DSUR

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Adverse Events (AEs)

All AEs should be recorded by the trial team in the medical notes as source data. They should also be captured in the Case Report Form (CRF) or the AE log CCTU/FRM006 which should be kept and filed in the TMF and/or Site file(s). AEs should be recorded for each trial participant.

7.2. Serious Adverse Events (SAEs) assessment

All AEs should be assessed by the Investigator for:

- Seriousness
- Expectedness of the event
- Causality between the investigational medicinal product(s) and/ or concomitant therapy and the adverse event.

7.2.1. Seriousness:

An Adverse event becomes serious if it:-

- Results in death
- Is life threatening*
- Requires hospitalisation or prolongation of existing inpatient hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other important medical event

**Life threatening in this case refers to an event where the subject's life was endangered at the time of the event. This is not an event that could have hypothetically caused death if it had been more severe.
This assessment is based on the medical judgement of the Investigator.*

7.2.2. Causality/Relatedness:

The CI/PI must make a decision on the causality/ relatedness of the event to the IMP. As per protocol, for example:

Relatedness	Expected	Unexpected
Definitely	SAR	SUSAR
Probably	SAR	SUSAR
Possibly	SAR	SUSAR
Unlikely	SAE	
Not Related	SAE	

Note: The CI and/or Sponsor cannot downgrade an Investigator's causality assessment, if the Sponsor disagrees that the event is related to the drug, clarification will be sought from the Investigator. If the Sponsor still disagrees both opinions must be provided with the report. Note that the same applies for the assessment by the Chief Investigator, who cannot downgrade a Principal Investigator's assessment of relatedness. However, up-grading is possible.

7.2.3. Expectedness:

The expectedness should be based on the information in the Protocol, Investigator's Brochure and/or the Summary of Product Characteristics.

Note: It is possible to list common expected side effects of an IMP clearly in the protocol and therefore with **prior agreement** from the Sponsor, Regulatory Authority and the REC, while those SARs still need to be recorded they can be excluded from the normal reporting process and timelines.

It is also possible to list SAEs which do not need to be recorded and reported (those known to be common in an underlying disease i.e. death in cancer)

Other Points to consider when assessing SAE/SAR/SUSARs:

- Could the event be as a result of a drug-drug interaction between the study IMP and a concomitant medication?
- Could the event be as a result of a reaction to a study placebo?
- Could the event be as a result of a reaction to a non IMP (NIMPs) also used in the trial?

All SUSARs associated with a comparator product in the clinical trial must be reported to the MHRA, the REC and the Sponsor as normal, **even if the product is authorised**. The Study team should also report SAEs associated with comparator products on the trial to the Sponsor as normal.

Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where SUSARs are causally associated with placebo (e.g. if the reaction due to an excipient), these should be reported as a SUSAR in the normal way.

Reactions to comparators or placebos that do not satisfy the criteria for a serious adverse drug reaction can also be reported as Other Important Medical Events if the Chief Investigator feels that this is appropriate.

7.3. Reporting Procedure

The minimum information required for reporting is:

- An identifiable subject (i.e.: initials, date of birth, sex and subject number).
 - A suspected investigational medicinal product
 - An identifiable reporting source (Centre ID or Site Number)
 - An adverse event assessed as serious and for which there is a reasonable suspected causal relationship.
 - The EudraCT number and/or Sponsor Trial identifier must be used in all submissions.
 - Date of onset of the event
1. This information is recorded using the SAE/R Reporting Form (CCTU/FRM 001), the original should be retained in the Case Report Form
A copy should be faxed or scanned and attached to emailed to the CCTU:

CCTU SAE Fax: 01223 256623

CCTU Email: cctu@addenbrookes.nhs.uk

2. The SAEs should be followed up until resolution. When follow up information is available a new SAE/R form should be completed with only the administrative details that would allow association with the original report and the follow up information

7.4. Receipt of a SAE from Participating Sites

For multi-centre trials it is the Chief Investigator's responsibility to forward all SAE forms received from participating sites to the CCTU

The Chief Investigator is also responsible for ensuring the follow-up of these events at their participating sites until solution

7.5. SAE Queries

- To minimise transcription errors the SAE Query Form CCTU/FRM002 will be customised for each trial and provided to the trial team by the CCTU
- SAEs queries can be processed via practice specified by the Trial Team or The SAE Query Form CCTU/FRM002. If using the CCTU customised form:
 - Create a reference number and record in the Query reference box on the SAE Query Form CCTU/FRM002
 - The query form must include the following information to assist identification of the SAE being queried:
 - The Patient Details
 - SAE Details
 - The query
 - SAE Form Field name
 - SAE Page No
 - Send the completed query form including a deadline either by:
 - fax or

- email (The SAE Query Form should be scanned or converted to PDF format and sent as an attachment)
- Query responses may need to be forwarded to the CCTU as the Sponsor representative for the purpose of Sponsor oversight

7.6. SAE Timelines

Action	Timeline
Reporting to the Coordinating site team from Participating sites	24 hours of Investigator awareness
Reporting SAE to Trust as Sponsor by sending it to CCTU	24 hours of Investigator awareness
Reporting SUSAR to Trust as Sponsor by sending it to CCTU	24 hours of Investigator awareness
Reporting SUSAR to REC & MHRA	7 days – fatal and life threatening 15 days – all others
Returning query responses to CCTU	As advised in query, depending on the nature of query and urgency

7.7. Suspected Unexpected Serious Adverse Reactions (SUSARs)

- All SAEs considered to be both related to the IMP and unexpected are identified as SUSARs and are subject to expedited reporting
- SAE's must be reported by the Chief Investigator to the MHRA, REC and Sponsor within statutory timelines (7 days for fatal and life threatening, 15 days for all others)
- Each SUSAR requires the entry of relevant data and information by the CI into the eSUSAR reporting system
- A SUSAR report can be printed off this system after completion
- Note that only CCTU staff or delegated Chief Investigators can report SUSARs to the MHRA. See eSUSAR Reporting Investigators Guide CCTU/GD003
- Reporting to the MHRA must not be done by participating site investigators
- The minimum regulatory requirements to be contained in the SUSAR documentation are:
 - An identifiable subject (i.e.: initials, date of birth, sex and subject number)
 - A suspected investigational medicinal product
 - An identifiable reporting source
 - An adverse event assessed as serious and unexpected and for which there is a reasonable suspected causal relationship.
 - The EudraCT number and/or Sponsor's protocol code must be used in all submissions

Note: for blinded and double blinded CTIMPs specific arrangements must be put in place on a trial by trial basis to verify if a potential SUSAR is in fact reportable.

7.8. Multicentre Trial SUSARs

- It is the Chief Investigators responsibility to alert other investigators that a SUSAR has occurred. This must be done in a timely manner and can be in the form of:
 - regular report
 - a newsletter/ safety alert
 - an email alert

7.9. Developmental Safety Update Reports

Refer to Developmental Safety Update Report CCTU/SOP003 for details.

7.10. Pregnancy

If a trial participant or partner becomes pregnant while on the trial, this must be reported to the sponsor (by sending the reports to the CCTU)

1. Once informed of the pregnancy of a trial participant or their partner when participating in a trial complete the Pregnancy Reporting Form
2. Forward to the CCTU as a scan or a fax:
 - CCTU Fax: 01223 256623
 - CCTU Email: cctu@addenbrookes.nhs.uk
3. The pregnancy must be carefully monitored with the consent of the mother
4. Any complications in the progression of the pregnancy should be reported as follow up information on a new form. Provide enough administrative details to identify the event and the participant and then only enter new information
5. Once the outcome of the pregnancy is determined, any untoward event may qualify as a Serious Adverse Event and the CI must assess for the causality of this event and relatedness to the study drug
6. If the treating Clinician decides that the adverse outcome was due to the trial drug the pregnancy becomes an SAR or even SUSAR and should be reported as such in the usual way

7.11. Other Important Safety Issues

Other safety issues which are subject to expedited reporting to the Sponsor by reporting to the CCTU include but are not limited to:

- Single case reports of an **expected** Serious Adverse Reaction which have an **unexpected outcome** (i.e. a fatal outcome)
- An increase in the rate of occurrence of an expected Serious Adverse Reaction, which is judged to be clinically significant
- Post trial SUSARs that occur after a participant has completed a clinical trial
- A new event relating to the conduct or the development of a clinical trial:

- A serious adverse event relating to trial procedures and which could modify the conduct of the trial
- Lack of efficacy of an IMP used for the treatment of life threatening disease
- A major safety finding from a newly completed animal study

In these cases:

- Complete CCTU/FRM004 Other Safety Issues and forward to the CCTU in a timely manner
- To report follow up information complete the administrative details to enable the event and the trial to be identified. Only record new information about this specific event
- If you are in any doubt of whether an event should be classed as an Other Safety Issue contact the CCTU who can facilitate prompt discussion and clarification with the Sponsor.

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system. Documents are reviewed every two years

9. References

The Institute of Clinical Research, 2008, Abbreviations used in Clinical Trials. The medicines for Human Use (Clinical Trials) regulations 2004

10. Associated Documents

CCTU/SOP003 Development Safety Update Report and the Annual Progress Report for Investigators

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document

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