Standard Operating Procedure CCTU/SOP002

Pharmacovigilance Process for Investigator Teams

1. Scope

For use by Chief Investigators and their delegates, working on Cambridge Sponsored CTIMPs that have been delegated the responsibility for pharmacovigilance by the Sponsor.

2. Purpose

To document the responsibilities delegated to the Chief Investigators and their delegates by the Sponsor.

To ensure that adverse events are appropriately recorded, reviewed, and reported to the Sponsor, 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.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Form	CCTU/FRM001for SAE/SAR/SUSAR in this SOP all are referred to as reporting form
ICSR submission portal	The central notification system for SUSARs reporting to the MHRA
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. An 'adverse event' is defined as per regulation 2(1) of the Clinical Trials Regulations.
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: Results in death Is life threatening Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability/incapacity Is a congenital anomaly/birth defect Is another important medical 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 on-going monitoring of the safety profile, combined with the on-going 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 participant and patients by ensuring that medicines put onto the market are safe.

3.2. Abbreviations

Abbreviation	Meaning
CUH	Cambridge University Hospitals NHS Foundation Trust
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Authority
nIMP	Non-IMP
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

4. Undertaken by

This SOP applies to Chief/Principal Investigators and their trial teams involved in the management of Cambridge Sponsored CTIMPs.

5. Items Required

- CCTU/FRM001 SAE/ SAR Reporting Form
- CCTU/FRM003 Pregnancy Reporting Form
- CCTU/FRM004 Other Important Safety Issues
- CCTU/SOP029 Data Transfer

6. Summary of Significant Change

- The Pharmacovigilance (PV) team is responsible for performing missing expectedness assessments and providing final confirmation of expectedness (Section 7.4.4).
- Requirements for the preparation and presentation of final Serious Adverse Event (SAE) and Pregnancy listings have been included (Section 7.12).
- Incorporation of updates to align with the Medicines for Human Use (Clinical Trials) (Amendment) 2025, UKSI 2025/538

7. Method

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

7.1. General Principles

- The Principal Investigator's causality assessment cannot be downgraded.
- The Chief Investigator can upgrade a PI's assessment

Reporting Timelines

Action	Timeline
Reporting to the CI from Participating sites	24 hours of Principal Investigator awareness
Reporting SAE/SAR to Sponsor by sending it to CCTU PV team	1 working day of Chief Investigator awareness
Reporting SUSAR to Sponsor by sending it to CCTU PV team (Initial and Follow up reports)	24 hours of Chief Investigator awareness
Initial reporting SUSAR to MHRA & and all Investigators concerned of relevant information by CI/delegate	7 days – fatal and life threatening 15 days – all others
Follow-up reporting SUSAR to MHRA & and all Investigators concerned of relevant information by CI/delegate	15 days all reports
Returning query responses to CCTU PV team	As advised in query, depending on the nature of query and urgency

7.2. Documentation

All events must be recorded using trial specific reporting forms. These will be generated by the PV team prior to trial initiation.

CCTU/FRM001 SAE/ SAR Reporting Form

CCTU/FRM003 Pregnancy Reporting Form

CCTU/FRM004 Other Important Safety Issues

7.3. Adverse Events (AEs)

- AEs should be recorded by the Investigator in the medical notes as source data. They should also be captured in the AE Case Report Form (CRF) which should be kept and filed as required by the protocol
- For blinded trials involving a placebo and an active drug, AEs should be evaluated as though the participant is receiving active drug
- Where an AE is classed as serious the trial specific SAE/ SAR reporting form (CCTU/FRM001) should be completed. SAE/SAR forms should be filed in the ISF and the TMF

7.4. Serious Adverse Events (SAEs) Assessment

All AEs should be assessed by the Investigator (or delegate) for:

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

7.4.1. 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 participant'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

Note: Per seriousness assessment type of SUSAR (7 days or 15 days) will be defined

7.4.2. Causality/Relatedness:

The PI or delegate must make a decision on the causality of the event to the IMPs/Comparator:

Relatedness	**Expected**	**Unexpected**

Definitely	SAR	SUSAR
Probably	SAR	SUSAR
Possibly	SAR	SUSAR
Unlikely	SAE	
Not Related	SAE	

Note:

- *If the CI/Sponsor disagrees with the PI assessment, both opinions must be provided with the report. Whilst the CI or Sponsor cannot downgrade a PI's causality assessment, they can upgrade it.*
- *All SAEs with missing causality will automatically be treated as SARs and an expectedness assessment will be completed in accordance with the approved RSI.*

7.4.3. Severity

- Severity is often used to describe the intensity of a specific event
- Severity assessments could be graded an intensity scale or CTCAE grading system. The Severity assessment grading needs to be indicated in the protocol
- Any worsening of severity should be captured as a NEW adverse event/SAE
- SARs should be assessed as unexpected if they are greater in severity than indicated in the RSI

7.4.4. Expectedness:

- Expectedness must be assessed against the trial specific reference safety information (RSI) that has been approved by MHRA
- If (in exceptional circumstances) the trial specific RSI was changed during the reporting period of an annual safety report (DSUR/APR in lieu of DSUR) the Trial Coordination team should inform the Sponsor (CCTU Pharmacovigilance team) regarding new RSI implementation date
- The RSI approved at the time of SAR onset must be used for expectedness assessment (relevant for late reports). SUSARs should not be downgraded on the basis that the RSI was updated after the occurrence of the event.
- Fatal and life-threatening SARs, including expected events, should not be considered as expected unless explicitly listed in the RSI
- SARs should be assessed as unexpected if they are different in nature or greater in specificity, or severity than indicated in the RSI
- The CCTU PV team will perform the expectedness assessment if it is missing from an SAE report
- The CCTU PV team will provide the final confirmation of the expectedness assessment for an event
- SAEs that are not related to the IMP, i.e. are not SARs, do not need an expectedness assessment against the RSI.

Note:

- *It is possible to list common expected side effects of an IMP clearly in the protocol. With prior agreement from the Sponsor and Regulatory Authority*

theses SARs can be excluded from the normal reporting process and timelines although they still need to be recorded

- *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 due to disease progression in cancer)*
- *Serious disease progression should be treated as an SAE unless explicitly excluded in the protocol*

7.4.5. Other Points to Consider When Assessing SAE/SAR/SUSAR:

- Where there is a possibility of interaction between a nIMP and an IMP, these events must be reported as SUSARs unless it explicitly outlined in the RSI(there is no need to report as a SUSAR if no any other drug interaction with the IMP is suspected)
- Could the event be as a result of a drug-drug interaction between the trial IMP, non IMP, comparator or a concomitant medication?
- It should be noted that investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to the marketing authorisation holder.
- Events associated with placebo usually will not satisfy the criteria for a serious adverse drug reaction and therefore will not require 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.
- Could the event be as a result of a reaction to a trial placebo?
- Reactions to comparators or placebos that do not satisfy the criteria for a serious adverse drug reaction can be reported as Other Important Medical Events if the Chief Investigator feels this is appropriate
- Has event severity or nature changed? If the nature or the severity of an event changes then this should be reported as a new separate event

Note:

- *Where it is not possible to determine whether a SUSAR is attributable to the Investigational Medicinal Product (IMP) or a non-Investigational Medicinal Product (nIMP), a precautionary (worst-case) approach should be adopted, and the event should be reported as a SUSAR associated with the IMP.*
- *Medical and scientific judgement should be applied when assessing and distinguishing between relevant and non-relevant information*

7.5. Reporting Procedure for Participating Sites

Principal Investigators at Participating sites are requested to report to the Chief Investigator as specified in the protocol.

The minimum information required for reporting is:

- Participant ID (i.e. date of birth, sex and participant 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 CTA number and/or Sponsor Trial identifier must be used in all submissions
  - Date of onset of the event
- This information is recorded using the trial specific SAE/SAR Reporting Form (CCTU/FRM 001)
- A copy should be scanned and attached to an email and sent to the appropriate addresses as specified in the protocol (usually to Chief Investigator and Trial Coordination team)
- The original is retained in the ISF

7.6. Reporting Procedure for Chief Investigators to the Sponsor

It is the Chief Investigator's responsibility to forward all reporting forms received from participating sites to the CCTU PV team.

- Following receipt of event information, the CI should review and assess the report, ensuring that causality, expectedness and seriousness have been provided correctly. Ensure that any patient identifiable information is redacted. Refer to CCTU/SOP029 Data Transfer
- Following assessment, events identified as SUSARs must be reported within the relevant timelines (see section 7.1 and 7.8)
- A copy of the reporting form should be emailed to the CCTU PV team CUH.CCTUPV@NHS.net
- Ensure the email subject line gives details of Trial, Participant ID and the coordinating site Event Reference Number
- The Chief Investigator is also responsible for ensuring follow-up of these events at their participating sites until resolution
- The investigator does not need to actively monitor participants for adverse events once the trial has ended, unless required in the protocol. Serious adverse events considered related to the IMP (i.e. SARs) occurring to a participant after the treatment of that participant has ended should be reported to the sponsor if the investigator becomes aware of them.
- Where an unreported SAE has been identified through monitoring activities or other discussions with the trial team, this should also serve as day zero (i.e. when the sponsor has first become aware of an SAE).

7.7. Event Queries / Follow-up

Event queries should be requested from participating sites by the trial team by email. Requests for information must include the following information to assist identification of the event being queried:

  - Participant ID
  - Event Name
  - Onset Date
  - Information requested
  - Any other relevant information

When a query response is received from a participating site:

- Document and retain with the original event data in the/ TMF along with SAE report form
- Forward to the CCTU as a follow-up report, within 24 hours of receipt

At the end of each month, coordination teams will receive their trial SAE listing which lists all SAEs with missing safety information or safety data discrepancies. The coordination team is expected to contact sites to retrieve the necessary information for all SAEs indicated in the listing.

7.8. Suspected Unexpected Serious Adverse Reactions (SUSARs)

**All SAEs considered to be both related to the IMP/Comparator and unexpected are identified as SUSARs and are subject to expedited reporting*

- The CCTU PV team will submit the SUSAR to the MHRA via the central notification system
- The narrative provided with the SAE report form will be used verbatim in the SUSAR report narrative section. The CCTU PV team will add no additional information, unless the reporting team provides additional clinical information, in which case, this too will be included verbatim
- A copy of the SUSAR submission will be provided to the trial team by the CCTU PV team

  The Chief Investigator/trial team is responsible for submission of each SUSAR to the Sponsor, PIs and to the IMP supplier/funder if applicable

**All SUSARs associated with Comparator product in the clinical trials must be reported to the relevant institutions, even if the product is authorised*

*** SUSARs and annual safety reports for all CTIMPs (whether they were submitted via Combined Review or not) will only be reported to the MHRA and trial PIs. If any ethical issues are identified by the MHRA when they receive these reports, they will liaise with the REC directly.*

- The minimum regulatory requirements to be recorded in the SUSAR documentation are:
  - Participant ID (i.e.: date of birth, sex and participant 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/CTA number and/or Sponsor's protocol code must be used in all submissions
- The SUSAR deadline date will be determined and confirmed by the CCTU PV team
- Safety of non-authorised non-IMPs (that should be used only exceptionally in clinical trials) should be reported in the same way as IMPs. Accordingly, SARs related to non-authorised non-IMPs should all be considered as SUSARs and should be reported to the licensing authority.

7.9. SUSARs in Blinded Trials

- For blinded CTIMPs, SUSARs must be unblinded prior to reporting to the MHRA and pharmaceutical company (if required by the contract)
- The CTC or designee not directly involved in the patient management, data-analysis or interpretation of results could perform unblinding. Similarly the CCTU PV Team can also perform SUSAR Unblinding if detailed in the protocol or Trial Procedures Manual
- Upon receipt of a SUSAR from a site, the CTC/designee will forward it to the CCTU PV team within 24 hours of the CI/CTC awareness
- Following receipt the CCTU PV team will review the form and request the CTC/designee to verify if a potential SUSAR is reportable
- The CTC/designee will unblind a participant's allocation following their own processes
- If after unblinding it is evident that the participant received the IMP, the CTC/designee will follow the procedures described in sections 7.7 and 7.8
- If after unblinding it is evident that the participant received a placebo the event would not require expedited reporting via ICSR system unless in the opinion of the PI the event was related to placebo (e.g. an allergic reaction to an excipient)
- To reduce the potential for bias occurring following a SUSAR, each trial must clearly document their procedures and the location of the unblinding information to ensure that all relevant trial personnel remain blinded

7.10. Pregnancy

If a trial participant or partner becomes pregnant while on the trial, this must be reported in accordance with the protocol.

All reports of exposure during pregnancy, medication errors, misuse or abuse in relation to the IMP should be recorded by the investigator and notified to the sponsor.

Once informed of the reportable pregnancy the CTC will:

- Ask the site to complete the Pregnancy Reporting Form CCTU/RM003 if they have not already done so
- Check the pregnancy report received from the site to make sure any pregnancy complications were reported
- Report pregnancy to the CCTU PV team CUH.CCTUPV@nhs.net

  **Follow up with the site to collect the pregnancy outcome in a timely manner*

  **A process should also be in place for following pregnancy outcome data in the event the end of trial has been declared but some outcome data is still pending.*

Note:

- *If the mother is not the trial participant consent must be obtained in order to closely monitor the pregnancy*
- *Any complications in the pregnancy should be reported as follow up information on a pregnancy form*

- *Any complications in the pregnancy that fulfils any serious criteria should be reported on an SAE reporting form. Provide enough detail to identify the event and the participant and then only enter new information*
- *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 trial drug*
- *If the treating clinician decides an adverse outcome was due to the IMP the pregnancy becomes a SAR or SUSAR and should be reported accordingly*

7.11. Multicentre Trial SUSARs

It is the responsibility of the CI to alert other investigators that a SUSAR has occurred. This must be done in a timely manner and can be in the form of:

- A regular report
- A newsletter/ safety alert
- An email alert

7.12. Other Important Safety Issues

Other safety issues which are subject to expedited reporting include but are not limited to:

- 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
- Follow CCTU/SOP019 Urgent Safety Measures and Temporary Halt for CTIMPs if applicable
- To report follow up information complete the details to enable the event and the trial to be identified. Only record new information about the 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

7.13. Commercial Organisation SUSAR Line Listings/Reports

Some commercially supported trials will receive SUSAR listings/reports as part of the Safety Data Exchange agreed prior to trial activation. These will relate to SUSARs reported from their own research programme:

- It is the CI's responsibility to review these fully in context of their trial

- The listing/report should be printed, signed & dated by the CI to confirm review and filed in the TMF
- Any findings relevant to the trial must be reported to the Sponsor via the Regulatory team PV email
- Trial documentation (eg protocol, PIS, Risk Assessment etc) must be reviewed as a priority, should any relevant findings be identified.
    - If an Urgent Safety Measure is triggered refer to CCTU/SOP019 Urgent Safety Measures in CTIMPs
- Any findings relevant to the trial must also be disseminated to all participating sites in a timely manner. It is not necessary to provide participating sites with the full listing/report, just the key messages and relevant supporting information/documentation
- Trial documentation must be amended in accordance with CCTU/SOP014 Amendment Management of CTIMPs

7.14. Final Serious Events and Pregnancy Data Listing

Before submission of the final listing the trial coordination team must check all potential sources of safety and pregnancy data, including recent or upcoming site closure activities and monitoring visits, to ensure all reportable events have been submitted to the CCTU PV team.

Any safety and pregnancy events identified during this review must be reported to the Sponsor/CCTU PV team immediately upon discovery.

The final safety and pregnancy listing will be distributed by CCTU PV team and will contain the final safety and pregnancy dataset. After final listing submission CCTU PV team does not anticipate receiving any further safety reports or updates.

The trial coordination team is responsible for filing the final SAEs and pregnancies line listing and the associated confirmation email in the clinical Trial Master File (TMF).

7.15. Development Safety Update Reports

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

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 and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

Reference Safety Information (RSI) for Clinical Trials- Part III (MHRA RSI Blog III) published 05 February 2021

Safety reporting. HRA/NHS amendments, published on 09 August 2024

Good pharmacovigilance practice (GPvP)

Good pharmacovigilance practice for medicines (GPvP) https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Guidance on changes to the clinical trials regulations - Health Research Authority

UK-specific annotations to ICH E6(R3) - GOV.UK

Pharmacovigilance - Health Research Authority

https://www.gov.uk/government/collections/medicines-clinical-trials#full-publication-update-history

https://medicover-mics.com/ich-gcp-e6r2-vs-e6r3-key-differences/

https://acrpnet.org/wp-content/uploads/2025/01/ICH-E6R2-to-ICH-E6R3-Comparison-01.28.25.pdf

10. Associated Documents

- CCTU/SOP003 Development Safety Update Report and the Annual Progress Report for Investigators
- CCTU/SOP019 Urgent Safety Measures and Temporary Halt for CTIMPs

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.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	CCTU/SOP002 V12
Local reference:	CCTU/SOP002 v13