Standard Operating Procedure CCTU/SOP061

SmPC, IB and Reference Safety Information Management in CTIMPs

1. Scope

This SOP applies to all trial teams running Cambridge Sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs).

2. Purpose

To ensure that SmPC, IB and Reference Safety Information is overseen and managed in accordance with the Sponsor's policies and current regulations and guidance.

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 the University of Cambridge (UoC); or jointly by CUH and UoC or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Investigator's Brochure	A document containing a summary of the clinical and non-clinical data relating to an Investigational Medicinal Product (IMP) that is relevant to the study of the product in human subjects. It contains information used for assessing the expectedness of an adverse reaction
Modifications	A modification (formerly amendment) is any change to an approved trial, categorised as substantial (Route A or Route B), an important detail, or minor, depending on its impact on participant safety, rights, or data reliability, each requiring different levels of review and approval from regulatory bodies.
Participating Site	Referred to in the regulations as a 'Trial Location' currently defined as: a hospital, health centre, surgery or wider healthcare setting, or facility or premises at or from which a clinical trial, or any part of such a trial, is conducted. For the purposes of CCTU SOPs, Forms and Templates, this does not include Participants homes.
Marketing Authorisation	A legally required, official approval granted by a regulatory authority—such as the MHRA—allowing a pharmaceutical company to sell a medicine. It confirms the product meets

	required safety, quality, and efficacy standards, defining its intended use, dosage, and patient population.
Reference Safety Information	Information in the product information relating to expected serious adverse reactions associated with an IMP, which is used to determine the adverse reactions that are to be treated as suspected unexpected serious adverse reactions in relation to that IMP. The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC section 4.8) or the Investigator's Brochure (IB). It is not the entire SmPC or IB.
Summary of Product Characteristics	This is the legal document approved as part of the marketing authorisation of a medicine which contains the definitive description of the product both in terms of its chemical, pharmacological and pharmaceutical properties, and its clinical use. Section 4.8 of the SmPC contains the reference safety information used to assess the expectedness of an adverse reaction.
Serious Adverse Reaction (SAR)	A Serious Adverse Event (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.

3.2. Abbreviations

Abbreviation	**Meaning**
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CTIMPs	Clinical Trial of Investigational Medicinal Product
CTA	Clinical Trial authorisation
DSUR	Development Safety Update Report
EU	European Union
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions

4. Undertaken by

The Chief Investigator and their research team involved in the management of Cambridge sponsored CTIMPs.

5. Items Required

CCTU/FRM105 SmPC/IB Review Form

6. Summary of Significant Changes

Updates in line with The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 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. RSI Selection for the Trial

The Reference Safety Information (RSI) must be identified for any Investigational Medicinal Product (IMP) and referenced during the course of protocol development with guidance from the Sponsor

The RSI must be clearly defined in the Protocol and the covering letter sent to the MHRA

For IMPs without a marketing authorisation in the UK, EEA or an ICH country

The RSI is contained in a specific section within the Investigator's Brochure (IB). This section should include a list of expected Serious adverse reactions (SARs), e.g. in the form of a table, where all related SARs are listed by MedDRA body System Organ Class (SOC) and Preferred Terms (PTs) , followed by frequency

For IMPs with a marketing authorisation in the UK, EEA or an ICH country, which are used according to MA

RSI is contained in section 4.8. 'Undesirable Effects' of the appropriate Summary of Product Characteristics (SmPC), where SARs are classified using PTs according to MedDRA, followed by frequency.

If it is proposed to use a licensed IMP outside the indication of MA within the trial, section 4.8 of the SmPC for the IMP still can be used as the RSI, if scientific justification is provided in the initial clinical trials application cover letter

If a scientific justification cannot be provided, then the RSI should always be a separated section within the IB

7.2. The RSI can be submitted in the following formats:

- A copy of the SmPC or IB for each IMP
- If the available SmPC(s) do not present the RSI in the expected format—for example, where SARs are not coded to MedDRA—a trial-specific RSI may be

submitted. This should be structured in accordance with the format recommended by the MHRA. If the IMP has a marketing authorisation in several EU member states, with different approved SmPCs, the Sponsor will justify its selection of the most appropriate SmPC (with reference to subject safety)

- In cases where a section of the IB is used as the RSI for IMP with a marketing authorisation (rather than section 4.8 of the SmPC), any differences between the list of expected ARs in the IB and the SmPC must be highlighted and their relevance to the trial fully justified
- Before an RSI can be used to assess expectedness of serious adverse reactions occurring in a trial it must be approved by the MHRA, this will initially be the RSI included in the CTA application. This must be used for the assessment of expectedness of any ARs that occur during the trial to define whether they meet the criteria for a SUSAR, until an updated RSI is approved by the MHRA via substantial modification. This requires several steps which are described in section 7.3

7.3. RSI Management during the Trial

- The CI/trial team is responsible for distribution of the approved version of the RSI to all relevant staff members at all participating sites to ensure that expectedness assessments are carried out appropriately
- Throughout the trial it is important that all participating sites use the same approved version of the RSI for expectedness assessment
- The CI is responsible for ensuring that a regular review of the SmPC/IB is performed to check whether there have been any updates to:
    - The overall safety profile of the IMP
    - The RSI section
- If a new version of the SmPC/IB is released, this must be formally reviewed and documented by the CI or a medically trained and delegated member of the trial team. Use CCTU/ FRM105 – SmPC/IB Review Form
- Where there have been changes, the new RSI must be reviewed against the current approved version to assess whether the changes affect the trial patients and whether the new RSI should be implemented within the trial
- Particular attention must be paid to any changes:
    - Which impact on trial processes and patient safety (e.g. eligibility, new contraindicated drugs, dosing levels)
    - To the section used for RSI
- This process must be completed for each new version of the SmPC or IB regardless of whether changes to the trial conduct or RSI are required
- Each new version of the SmPC/IB must be printed, attached to CCTU/ FRM105 – SmPC/IB Review Form and filed in the TMF
- If a decision is made that an update to the RSI content is necessary then the new updated version of the RSI must be submitted to the MHRA as a substantial modification

  Note: Depending on the type of the RSI update, Route A (e.g. new expected events added) or Route B (e.g. an increase in frequencies with no new expected events added) substantial modifications should be submitted

to the MHRA (For further information refer to the MHRA guidance on the various types of modifications and collection, verification, and reporting of safety events in clinical trials.)

- If the protocol and/or patient documents are to be modified in-line with the new updated SmPC/IB and/or RSI they need to be submitted as a substantial modification to the MHRA and REC/HRA as required
- The implementation date of the new RSI must be clearly defined in the covering letter to the MHRA as part of the modification. It must also be made explicitly clear to all participating sites when provided to them for C&C approval
- Any urgent safety updates must be implemented as soon as possible refer to CCTU- SOP019_Urgent Safety Measures
- Once the substantial modification is approved, the CI must ensure that all participating sites are notified of the modification so that the new documentation can be approved locally ready for implementation on the specified date
- The previous version of the RSI must be appropriately superseded in the TMF and ISF
- If all trial participants have completed trial treatment and the SAE reporting duration for the trial as determined by the protocol is passed then there is no need to perform any further RSI reviews. This should be documented in a file note and placed in the RSI review section of the trials master file. A copy of the file note must be sent to the CCTU regulatory team to be filed in the trial Sponsor file. If you are unsure, please seek advice from the CCTU regulatory team

7.4. Updated RSI - Impact on DSUR Reporting

For the purposes of the DSUR SAR listing the version of the approved RSI in use at the start of the reporting period must be used for the classification of SARs for the entire period

Changing the RSI in the middle of the DSUR reporting period may result in certain SARs no longer being reported as SUSARs and visa-versa

To avoid reclassification of SARs for the DSUR you can choose, at the point of submitting a modification to the MHRA, to continue with the current RSI for the remainder of the DSUR reporting period if this is appropriate.

This must be made explicitly clear in the MHRA modification covering letter in the form of the implementation date

7.5. Other SmPC/IB changes

- If a decision is made that no update to the RSI is necessary but that there have been updates to the SmPC/IB sections incorporating drug management and administration, Eg a change to
    - The drug storage conditions
    - The drug handling details
- Participating site staff must be made aware of the changes

- The pharmacy manual (CCTU/TPL066) should be updated in line with the changes. This should be discussed with the trial pharmacist
- The updated pharmacy manual should be sent to all participating sites

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

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538

MHRA guidance: Clinical trials for medicines: collection, verification and reporting of safety events

MHRA guidance: Clinical trials for medicines: modifying a clinical trial approval

CT1 EC Guidance 2010/C 82/01 "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial"

CT3 EC Guidance 2011/C 172/01 "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use"

ICH Harmonised Tripartite Guideline for Development Safety Update Report E2F

10. Associated Documents

CCTU/SOP003 Developmental Safety Update Report for CTIMPs

CCTU/SOP002 Pharmacovigilance Process for Investigator Teams

CCTU/SOP014 Modification Management of CTIMPs by Trial Teams

CCTU/SOP019 Urgent Safety Measures

CCTU/TPL066 Pharmacy Manual

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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