Standard Operating Procedure CCTU/SOP019

Urgent Safety Measures and Temporary Halt for CTIMPs

1. Scope

This SOP applies to all Cambridge Sponsored CTIMPs regulated by The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/583 and subsequent amendments.

2. Purpose

To detail the procedures to be followed if unexpected events occur relating to the conduct of a Cambridge-Sponsored trial (or the development of an IMP) that necessitate the Sponsor or Investigator taking appropriate Urgent Safety Measures to protect trial participants against any immediate hazard to their health or safety.

This SOP also gives guidance on how to temporarily suspend a trial.

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
Urgent safety Measures	An action that the sponsor or investigator may take in order to protect the participants of a trial against any immediate hazard to their health or safety
Temporary halt	Stoppage to a trial that was not envisaged in the approved protocol and there is intention to resume it, it does not however include temporary halt of trial for logistical reasons

3.2. Abbreviations

Abbreviation	Meaning
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CTIMPs	Clinical Trials of Investigational Medicinal Products
CTO	Clinical Trial Officer
HRA	Health Research Authority

IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Product Regulatory Agency
NRES	National Research Ethics Service
R&D	Research and Development
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USM	Urgent Safety Measures

4. Undertaken by

This SOP applies to staff involved in Cambridge Sponsored CTIMPs.

The CI of a Cambridge Sponsored CTIMP has been delegated the responsibility to take appropriate Urgent Safety Measures.

The CCTU regulatory team is responsible for submitting substantial amendments to the MHRA using the submission portal for trials not submitted via combined review

5. Items Required

- MHRA website for up to date reference on Urgent Safety Measures and temporary halt:
  - Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK
- HRA website for up to date reference for Urgent Safety Measures:
  - Safety reporting - Health Research Authority
- CCTU/SOP004 End of Trial Procedures
- CCTU/SOP014 Modification Management of CTIMPs by Trial Teams
- CCTU/FRM014 Contact Telephone Report
- CCTU/FRM004 Other Important Safety Issue Reporting Form
- Modification Tool

6. Summary of Significant Changes

Update to in relation to 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.

Urgent Safety Measures on the MHRA/HRA websites should always be consulted when using this SOP

7.1. When to take Urgent Safety Measures

- Urgent Safety Measures should be taken in a clinical trial when it is considered that they are required in order to protect clinical trial participants from any immediate hazard to their health and safety
- Urgent Safety Measures should be implemented immediately, approvals are not required prior to implementation

Examples of when Urgent Safety Measures may be Required

- An increase in the rate of occurrence of an expected SAR, which is judged to be clinically important
- Post-study SUSARs that occur after the participant has completed a clinical trial
- A new event relating to the conduct or the development of the IMP likely to effect the safety of the participants e.g.;
    - A serious event which could be associated with the trial procedures and which could modify the conduct of the trial
    - Lack of efficacy of an IMP used for the treatment of a life-threatening disease
    - A major safety finding from a newly completed animal study

7.2. Actions

- The CI is delegated the responsibility to take appropriate Urgent Safety Measures
- The CI must notify the MHRA, REC and Sponsor as detailed in sections 7.2.1 – 7.2.3 below
- Necessary treatments and participant recruitment should be put on hold until there is evidence to suggest that the trial is safe and can be restarted 7.4
- If Urgent Safety Measures (USM) need to be taken during a period in which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health then the MHRA, REC and Sponsor must be informed as soon as possible

7.2.1. Notifying the MHRA

- The CI should telephone the Clinical Trials Unit at the MHRA and discuss the issue with a safety scientist immediately (i.e. within 24 hours of measures being taken)
- This conversation should be documented (CCTU/FRM014 Contact Telephone Report) and filed within the TMF for future reference
- For studies not originally submitted via the combined review process: The CI must give written notice to the MHRA of the Urgent Safety Measures by emailing the medical assessor who assessed the USM over the phone, within seven days of implementation
- For studies submitted through the combined review process: The CI must submit the USM written notification via new IRAS, within seven days of implementation of measures

- A medical assessor may contact the CI should further clarification be required
- Notification of a substantial modification (formally termed amendment) is also required within 2 weeks of notification to the MHRA (refer to CCTU/SOP014 Modification Management of CTIMPs by Trial Teams), which should include:
    - A covering letter detailing:
    - The measures taken
    - The reason for them
    - The name of the safety scientist contacted
    - The modification tool
    - Any supporting documentation
- Modification documentation must be reviewed and authorised by the CTO
- The USM-related substantial modification must not include changes different from those required as an urgent safety measure

For CTIMPs not originally submitted through the combined review process:

- The CTO will submit the substantial modification to the MHRA and will send an e-mail to confirm submission to the trial team with all uploaded documents

For CTIMPS originally submitted through the combined review process:

- The trial team will submit the substantial modification to the MHRA via new IRAS (the modification will also submit to the REC at the same time)

7.2.2. Notifying the REC

For CTIMPs not originally submitted through the combined review process:

- The CI must notify the REC of the Urgent Safety Measures by email within 7 days of implementation of measures, setting out:
    - The reasons for the Urgent Safety Measures
    - The plan for further action

For CTIMPS originally submitted through the combined review process:

- No separate REC notification is required; this will have been done when the CI notified the MHRA of the USM in new IRAS

For all trials, if the urgent safety measure merits a substantial modification to the documentation to be approved by the REC this must be submitted within 2 weeks of notification to the MHRA. The modification should be marked as being in response to urgent safety measures

Refer to CCTU/SOP014 Amendment Management of CTIMPs by Trial Teams

7.2.3. Notifying the Sponsor

- The CI must notify the CCTU (acting on behalf of the Sponsor) using the Other Important Safety Issue Reporting form CCTU/FRM004 and emailing this to cuh.ccturegulatory@nhs.net immediately following implementation of measures, setting out:
    - A description of the safety issue

  - The details of the measures taken
  - The reasons for the measures
  - Confirm that the MHRA and REC have been informed
  - Confirm that other PI's have been contacted as required
- The substantial modification must be submitted immediately, refer to CCTU/SOP014 Modification Management of CTIMPs by Trial Teams
- The CI should keep CCTU informed of the progress, outcome or resolution of the actions taken by sending follow-up Other Important Safety Issue Reporting Form(s) CCTU/FRM004

7.2.4. Notifying all Sites

- The CI should inform all participating sites and Principal Investigators of the implementation of Urgent Safety Measures immediately or within a maximum of seven days in writing by email
- The local Principal Investigator must carry out the actions at their participating site

7.2.5. Notifying Trial Participants

- Trial participants must be informed of the Urgent Safety Measures and be given the option to continue in the trial with the modified trial procedures or withdraw.
- Trial participants must be informed in writing of:
  - The rationale for the Urgent Safety Measures
  - The steps taken or new procedures required to minimise the risks
- The necessary actions must be appropriate to the measures implemented and will be determined by the CI in conjunction with the CCTU (acting on behalf of the Sponsor), for example:
  - Requirement to re-consent to an updated participant information sheet and/or
  - Provision of study update letter to participant in lieu of an updated PIS

7.3. Documents that must be Retained

- All communications relating to the measures should be retained e.g. emails, memos, or letters and filed in the TMF and the sponsor's trial files.

7.4. Temporary Halt of a Trial

- Temporary halt to a trial is sometimes necessary for various reasons, including Urgent Safety Measures. Temporary halt can apply to:
  - The whole trial
  - At individual site(s)
  - All Cambridge Sponsored trials using the same IMP; and can halt recruitment and/or interrupt treatments of active participants
- The notification of temporary halt should:

  - Be submitted to both the REC and MHRA as a substantial modification within 15 days from when the trial is temporarily halted
  - Detail what is being halted and reasons for the temporary halt
- When there is evidence to suggest the trial is safe to recommence:
  - A request to re-start the trial should be submitted as a substantial modification
  - Provide necessary evidence
- Refer to CCTU/SOP014 Modification Management of CTIMPs by Trial Teams

7.5. Permanent Halt of a Trial

- Should the Sponsor or Investigator decide the trial will not recommence after temporary halt, an End of Trial Declaration notification must be submitted within 15 days of the decision
- Refer to CCTU/SOP004 End of Trial Procedures

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

- Common Abbreviations and Definitions CCTU/INF001
- The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025
- Note: The MHRA web-pages on Urgent safety measures should always be consulted when using this SOP: Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK
- Note: The HRA web-pages on Urgent safety measures should always be consulted when using this SOP: Safety reporting - Health Research Authority
- When is a clinical trial halt not a clinical trial halt? – MedRegs

10. Associated Documents

R&D/SOP001 CTIMP Delegation of Roles & Responsibilities

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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