

Standard Operating Procedure CCTU/SOP004

End of Trial Procedures (CTIMPs)

1. Scope

This SOP applies to staff working in Research and Development (R&D) the Cambridge Clinical Trials Unit (CCTU) staff, Chief Investigators (CIs) and Principal Investigators (PIs) within the Trust (either as substantive employees or under an honorary contract) involved with, or working on Trust sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs).

2. Purpose

This SOP covers the end of trial or early termination declarations, site closure, end of trial reports, and outlines the process to ensure the CCTU maintains oversight of these activities.

This process ensures that all clinical trial related activities are appropriately reconciled, recorded and reported in accordance with the protocol, SOPs, ICH-GCP and the applicable regulatory requirements.

It is integral to the quality assurance of clinical trials to ensure the integrity of the trial should it be necessary for the information to be retrieved or inspected in the future.

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
Archiving	The process of preparing and storing documents for a defined period of time to preserve their integrity and readability
End of Trial	The date of the last visit of the last participant or the completion of any follow-up monitoring and data collection as described in the protocol.
Essential Documents	Those documents that individually or collectively permit the evaluation of the conduct of a trial and the quality of the data generated. Essential Documents include the Trial Master File, source documents, Case Report Forms, Sponsor File and the Pharmacy File. (section 8, ICH-GCP E6 (R1)).

Investigational Medicinal Product IMP	The IMP is the pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is for the purposes of the trial: a) used or assembled (formulated or packaged) in a way that differs from the form of the product authorised under the Marketing Authorisation b) used for an indication not included in the summary of product characteristics (SmPC) under the Marketing Authorisation for that product or c) used to gain further information about the form of that product as authorised under the authorisation
Investigator Site File ISF	The Investigator Site File is a standard filing system which allows the effective storage and location of Essential Documents relating to the conduct of the trial at the Participating Site. As with the TMF, the filing system can be in the form of a single project file or a number of files as deemed appropriate. The ISF also encompasses the Participating Site Pharmacy Files.
Pharmacy File	The Pharmacy File is a standard filing system which allows the effective storage and location of Essential Documents relating specifically to IMP Management and Dispensing Procedures.
Sponsor File	The Sponsor File comprises a selection of Essential Documents for the trial, which confirms compliance with sponsor's governance procedures and provide evidence of Sponsor oversight and management of the trial.
Trial Master File TMF	The Trial Master File is a standard filing system which allows the effective storage and location of Essential Documents. The filing system can be in the form of a single project file or a number of files as deemed most appropriate. The TMF also encompasses the Pharmacy Files and Site Information in TMF: Site Information
TMF: Site Information	Participating site information and local essential documents held by the co-ordinating centre, though technically part of the TMF, these files are often held separately for ease of use.

3.2. Abbreviations

Abbreviation	Meaning
CTIMP	Clinical Trial Investigational Medicinal Product
ISF	Investigator Site File
PS	Participating Site
ReDA	Research Data Base Application
SmPC	Summary of Product Characteristics
TMF	Trial Master File

4. Undertaken by

The Chief Investigator is responsible for:

- Declaring the end of trial as defined in the protocol
- Completion and timely submission of the end of trial notifications to the relevant body

- Closure of all Participating Sites in the trial, including provision of documentation for the Investigator Site File
Generation of the End of Trial Report within 12 months of the End of Trial Declaration
- Archiving of the Trial Master Files (including the Pharmacy File and TMF: Site Information)
- Ensuring that all trial publications are notified to the CCTU and ensuring these are filed/archived as appropriate
- Ensuring that all Participating Sites have been closed-out appropriately

The CCTU is responsible for:

- Obtaining all end of trial documentation and updating the trial tracking tools
- The close-out visit at Addenbrooke's (Local Site)
- Ensuring the completeness of the Sponsor file
- Ensuring the End of Trial Reporting timelines are adhered to
- Archiving the Sponsor file documentation

5. Items Required

CCTU/SOP006 Archiving Procedure

Research Governance Training Manual

Structure and content of clinical study reports (CPMP/ICH/137/95)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002832.pdf

CCTU/SOP027 Data Management

6. Summary of Significant Changes

Requirements for the closure of Participating Sites

7. Method

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

7.1. Notification of End of Trial or Early Termination

- The Chief Investigator (CI) notifies the MHRA, REC and the CCTU of any trial that has been completed according to the definition of the end of trial in the protocol or that has been terminated prematurely
- For multi-centre trials the notification is only completed when the trial has closed at all sites

Notification should be as follows:

For end of trial (completed) within 90 days of the end of the trial

For early termination within 15 days with a reason for the termination

- CI completes the Declaration of End of Trial Form
- This form is available from the EudraCT website at:
<https://eudract.ema.europa.eu/document.html>
- Copies of the following documents should be sent to the CCTU for inclusion in the Sponsor files and to participating sites for inclusion in the ISF:
 - Notification to the MHRA & Covering Letter
 - Notification to the REC & Covering Letter
 - Copies should also be filed in the relevant sections of the TMF
 - Acknowledgements of receipt from both the REC and MHRA
- The CCTU will send copies of acknowledgements of receipt from the MHRA to the R&D Finance team
- The CCTU will also send copies of the REC and MHRA Acknowledgements to the R&D Department

7.2. Participating Site Closure

- The PS may only be closed once all data queries have been answered and resolved and documentation returned to the coordinating site as necessary
- Once all documents have been provided to the Participating Sites for inclusion in the ISF the CI or designee will arrange for a Close-out Visit or Teleconference as appropriate
- A Close Out Monitoring Report (template available) should be completed for all Close-out Visits or
- A Remote Monitoring Report (template available) should be completed by the PS and returned to the Coordinating Site in advance of the TC
- During the Close-out visit or TC specific attention should be paid to:
 - IMP Accountability including the return or destruction of IMP which was provided specifically for use in the trial (not hospital stock)
 - Confirmation of archiving arrangements for the ISF and associate files at the PS
 - Any discrepancies in the ISF documentation and arrangements for resolution
 - Any specific requirements of the site staff including the publication rights and procedures, dissemination of information to trial participants etc.
 - Any ongoing responsibilities of the site staff or the site for example collection of patient long-term follow-up data, provision of information in the event of an Audit or Inspection or long term safety reporting for patients included in the trial

7.3. Addenbrooke's (Local) Site Closure

- Once all the documentation has been received by the CCTU the end of trial details will be entered onto all trial tracking tools as appropriate
 - CCTU ReDA
 - MHRA eSUSAR website
- All studies that have obtained/received IMP will be closed out even if no subjects were recruited
- The close-out visit will be performed as soon as is practical after the Declaration of an End of Trial form is submitted to the CCTU
- A single final close out visit report will be completed
- Close-out visits will be conducted by the Clinical Trials Monitors
 - this can be delegated or contracted out to external organisations/monitors
 - Oversight will be retained by the CCTU

7.4. The Close Out Visit (Addenbrooke's Local Site Only)

The Clinical Trials Monitor will:

- Confirm with the trial team and the CI, the scope and anticipated duration of the close-out visit by email
- Request access to the TMF, ISF and Pharmacy Files in order to complete the close-out visit
- Complete a review of the documentation in the Sponsor file, (electronic & hardcopy) to ensure that all relevant documentation is present
- Request any outstanding documentation for the Sponsor file during the close-out visit
- Will complete the Close-out Monitoring Visit Report CCTU/FRM009
- Send out a Close-out visit follow-up letter to the Chief Investigator
- File a copies in the Sponsor file and the TMF

The Assistant Director of the CCTU or Designee will:

- Review the report and feedback any comments or actions requested by the monitor
- Sign the completed final copy of the visit report to be filed in the Sponsor File

Outstanding Actions

- Resulting from the close-out visit will need to be completed and documented within an agreed timeframe

7.5. End of Trial Report

- All correspondence with the MHRA and REC must be retained in the TMF and copied to the Sponsor

- The end of trial report is due within 12 months of the Declaration of End of Trial and is submitted to the REC, MHRA and the CCTU
- There is no standard format for End of Trial Reports. The GCP guidance document called "structure and content of clinical study reports" (CPMP/ICH/137/95), which can be found under:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002832.pdf
- As a minimum the MHRA, REC and Sponsor requires information on:
 - Title of the trial
 - Name and address of the sponsor or sponsoring group's legal representative in the UK
 - EudraCT number
 - Trial Protocol code number if any
 - The investigational medicinal product(s) (IMPs) tested in the trial
 - Date of end of trial
 - Date of end of complete trial in all participating centres in all countries within and outside the EU if relevant. Note: specific requirements may vary across different countries
 - Whether the project achieved its objectives
 - The main findings
 - Arrangements for publication
 - Dissemination of the research including feedback to participants

7.6. Trial Publications

- All publications should be sent to the CCTU with a copy placed in the TMF and Sponsor file
- For any publication or dissemination of clinical trials and clinical research follow the guidance given by CONSORT, which stands for Consolidated Standards of Reporting Trials, found under <http://www.consort-statement.org/consort-statement/>

7.7. Archiving

- The trial may only be archived once all the End of Trial Documentation and End of Trial Reports have been written, submitted and filed accordingly
- Any publications received after the files have been archived will be added to the archive at that time
- The trial documentation must be archived in accordance with EU Clinical Trial of Investigational Medicinal Product Archiving CCTU/SOP006

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.
<https://eudract.emea.europa.eu/document.html>

10. Associated Documents

See section 5

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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