Standard Operating Procedure CCTU/SOP004

End of Trial Procedures for Cambridge Sponsored CTIMPs

1. Scope

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

2. Purpose

This SOP outlines processes to ensure that the CCTU maintains oversight of the end of trial or early termination declarations, site closure, end of trial reports and publications.

This process ensures that clinical trial related activities are appropriately reconciled, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements to ensure the integrity of the documentation should the information 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.

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
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, investigator site file, source documents, case report forms, sponsor file and the pharmacy file. (Section 8, ICH-GCP E6 (R1).
Investigational Medicinal Product	The IMP is the pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial.

(IMP)	This includes a medicinal product which has a marketing authorisation but is for the purposes of a clinical 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 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 that allows the effective storage and location of essential documents relating to the conduct of a clinical trial at a participating site. The filing system can be in the form of a single project file or a number of files. The ISF also encompasses the participating site pharmacy files.
Pharmacy File	The pharmacy file is a standard filing system that allows the effective storage and location of essential documents relating specifically to IMP management and dispensing procedures.
Sponsor File	The sponsor file comprises of the essential documents that confirm compliance with the Sponsor's governance procedures. This provides evidence of Sponsor oversight and management of a clinical trial.
Trial Master File (TMF)	The trial master file is filing system that allows the effective storage and location of essential documents relating to the conduct of a clinical trial. This can be in the form of a single project file or a number of files. The TMF also encompasses the pharmacy files and the site information file for every participating site involved in a clinical trial
TMF: Site Information	Participating site information and local essential documents held by the co-ordinating centre. Technically part of the TMF, these files can be held separately for ease of use.

3.2. Abbreviations

Abbreviation	**Meaning**
CONSORT	Consolidated Standards of Reporting Trials
CTC	Clinical Trials Coordinator
CTIMP	Clinical Trial Investigational Medicinal Product
EPIC	Electronic Patient Record
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PS	Participating Site
ReDA	Research Data Base Application
REC	Research Ethics Committee
SDV	Source Data Verification
TMF	Trial Master File

4. Undertaken by

The Chief Investigator (CI) is responsible for:

- Declaring the end of trial as defined in the protocol
- Completion and timely submission of end of trial notifications in accordance with regulatory timelines:
    - Submitting the completed end of trial declaration form to the CCTU regulatory team
    - Forwarding the completed end of trial declaration form to REC for non-combined review trials
    - For trials submitted via combined-review, submitting the end of trial from in the new part of IRAS
- Ensuring the provision of documentation for the Investigator Site File at all participating sites in the trial
- Ensuring that all participating sites including CUH have been appropriately fully closed out. For multi-centre trials, the clinical trials coordinator will close down the CUH site except pharmacy. (CUH pharmacy will be closed out by the sponsor assigned clinical trial monitor as this will also cover sponsor pharmacy aspects)
- Completing analysis of trial data and generating the end of trial report/summary of results dataset within the regulatory timeframe from the date the trial concluded as recorded on the end of trial declaration
- Providing the Regulatory Team with a copy of the final report and copy of the confirmation email to the MHRA that the summary of results has been published on the clinical trial registry
- Archiving of the TMFs, including the TMF Site Information files following receipt of the Sponsors End of Trial Confirmation Letter
- Ensuring that all trial publications are notified to the CCTU and ensuring these are filed/archived as appropriate
- Managing the research samples long-term storage or destruction according to details stated in the IRAS application

The CCTU Regulatory Team is responsible for:

- Obtaining all end of trial documentation and updating the trial tracking tools
- Making the EoT Declaration submission to MHRA on behalf of the Sponsor for trials not submitted via combined review
- The close-out visit at the CUH pharmacy, TMF and central facilities
- Ensuring the completeness of the Sponsor Files
- Facilitating adherence to the end of trial reporting timelines
- Providing the final safety data set for Sponsor reported SAEs, SARs & SUSARs (as applicable)
- Archiving the Sponsor File documentation

5. Items Required

CCTU/TPL069 Close-Out Monitoring Report

CCTU/GD008 Monitoring Activities Guidance Document

CCTU/TPL099 Participating Site Close out Template
CCTU/SOP044 Research Sample Management
CCTU/FRM097 Hard Lock Completion Confirmation
CCTU/SOP 058 Randomisation using Sealed Envelope.
CCTU/GD059 Registering Clinical Trials
CCTU/SOP011 Monitoring Trust Sponsored CTIMPs
CCTU/GD066 Remote Monitoring Guidance for the Central Coordination Team
CCTU/TPL098 Remote Monitoring Conversation Template
CCTU/FRM117A End of Trial Checklist for CCTU Managed Trials
CCTU/FRM117B End of Trial Checklist for CCTU Managed Participating Sites
CCTU/TPL101 Participating Site Closing Letter

6. Summary of Significant Changes

- Inclusion of the requirement for CI and CTCs, where appropriate, to review the final end of trial results before wider dissemination
- Requirement for any serious breaches to be included in publications
- Update to the email subject line and details to notify the MHRA when the end of trial summary of results has been published on a public register(s)
- Pharmacovigilance (PV) team actions added
- Removal of references to EudraCT

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

- It is the CI's responsibility to declare a trial completed when it reaches the end of trial as defined in the protocol or it has been terminated prematurely in accordance with the timeline listed below
- All trial activities (including all protocol stated follow-up visits and procedures) must be completed before the trial can be declared completed to both the MHRA and REC. Separate early closure to the MHRA is not permitted
- For multi-centre trials the notification is only submitted when the trial has completed at all sites
- For multi-national trials, the end of trial form should only be submitted when the trial has ended in all countries
- For CTIMPs that were not submitted through combined review, the Chief Investigator (CI) or delegate will complete the Declaration of End of Trial Form available on the MHRA website:
  https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial

Timeline for notification:

  - 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

End of trial notification to REC (for trials not submitted through combined review)

The CI or delegate will:

- Submit the notification (Declaration of End of Trial Form and cover letter) to the REC
- File the notification, submission email and subsequent acknowledgement of receipt in the relevant section of the TMF
- Provide copy of the notification, submission email and acknowledgement of receipt to the CCTU for inclusion in the Sponsor File

End of trial notification to MHRA (for trials not submitted through combined review)

The Regulatory Team will:

- Submit the notification (Declaration of End of Trial Form and cover letter) to the MHRA upon receipt of the necessary documentation from the CI or delegate
- File the notification, covering letter and proof of submission
- Provide copy of documents to the CTC for inclusion in the TMF

End of trial notification for trials submitted through combined review

The CI or delegate will:

- Submit the EoT notification in the new part of IRAS. This automatically submits the notification to the REC and MHRA
- Provide a copy of the Declaration of End of Trial Form and cover letter, and subsequent emails and acknowledgement of receipt to the CCTU for inclusion in the Sponsor File

Notification to CUH R&D, Participating Sites & Other Organisations:

The CI or delegate will provide copy of end of trial notification documents to CUH R&D, participating sites for inclusion in the ISF and to other organisations as defined in contractual agreements

7.2. Participating Site Closure

- The PI is responsible for ensuring that the medical records for all patients linked to the trial are marked as completed/withdrawn prior to the close-out visit
- The Participating Site including the lead site (CUH) may only be closed when all data queries have been answered, resolved and documentation returned to the coordinating team as necessary
- Site pharmacies can be closed ahead of the full site closure; this is recommended particularly when trials have a long duration between the last patient last treatment visit and the last patient last visit (trials with a long-term follow-up). If you are unsure if this is relevant, discuss this with the CCTU Regulatory team

- Once all the documents have been provided to the participating sites for inclusion in the ISF, the CI or designee will arrange for a site close-out via: Remote monitoring Refer to CCTU/GD066 Remote Monitoring Guidance for the Central Coordination Team
    - The coordinating team will distribute The Participating Site Close Out Template CCTU/TPL099 to participating sites (including CUH for multicentre trials) for completion, along with an electronic copy of all essential documentation for the duration of the trial so that the site team can perform an ISF reconciliation as needed prior to archiving
    - Upon receipt, Participating sites are expected to complete and return the completed form in advance of site closure
- On-site visit
    - The Close out Monitoring Report CCTU/TPL069 should be completed for all site closeout visits.
        - In single centre trials where CUH is the only site, an on-site close out visit will be performed by the assigned Clinical Trial Monitor
- During close out procedures, specific attention should be paid to:
    - IMP accountability including the return or destruction of IMP which was provided specifically for use in the trial (this excludes hospital stock)
    - Confirmation of archiving arrangements for the ISF and associate files at the PS
    - Closure of trial documents such as the final non-compliance log and fully signed-off Delegation Log
    - Specific requirements of the site staff including the publication rights and procedures, dissemination of information to trial participants etc.
    - On-going 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. Central Trial Activities Closure (TMF, CUH Pharmacy & Central Facilities closure)

- All outstanding monitoring findings from previous monitoring activities and compliance with the monitoring plan, specifically levels of SDV and verification of query resolution need to be completed prior to final data cleaning and database lock
- Once all the documentation has been received by the Regulatory Team the end of trial details will be entered onto all trial tracking tools as appropriate
    - ReDA
- All studies that have obtained/received IMP will be closed out even if no subjects were recruited
- Close-out visits for the trial (TMF, CUH pharmacy, central facilities) will be conducted by Clinical Trials Monitors or where this is delegated or contracted out to external organisations/monitors, the Regulatory Team will maintain oversight by reviewing completed close-out reports prepared by external/contract monitor

- The central trial team will file final safety data line listing and emails in the TMF

The Clinical Trials Pharmacovigilance Officer will:

- Confirm with the trial team/CI that all safety reporting and updates are complete
- Finalise the safety data cleaning and reconciliation for the trial
- Provide the trial team with an email containing the full and final safety line listing for the trial

The Clinical Trials Monitors will:

- Confirm with the trial team and the CI, the scope and anticipated duration of the closeout visit by email
- Request access to the TMF, ISF (for single centre trials) and pharmacy files in order to complete the closeout visit
- Follow the review process detailed in CCTU/SOP011
- Complete the Close-Out Monitoring Report CCTU/TPL069
- Ensure that the final non-compliance log is printed and signed by the CI at the final closeout visit
- Send a closeout visit follow-up letter to the Chief Investigator/PI & trial team and Pharmacy
- File a copy of fully signed report and follow up letter in the Sponsor File
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7.4. Outstanding Monitoring Actions

- Outstanding actions from the closeout visit must be completed and documented within an agreed timeframe as detailed in the follow up letter.

7.5. Sample Handling

- Refer to CCTU/SOP044 Research Sample Management.
- The CI or delegate will inform any labs involved in processing storage or analysis of samples that the trial has closed
- Within one year of the conclusion of the trial The CI or delegate will ensure research samples are either stored, transferred to another ethically approved study or destroyed according to the requirements stipulated in the clinical trial protocol and IRAS form.

7.6. End of Trial Reporting

- The CI will confirm that they are satisfied with the trial database locking process by completing and signing the Hard Lock Completion Confirmation form CCTU/FRM097. This is filed in the TMF
- It is the CI's responsibility to ensure analysis is completed and the summary of results report has been appropriately reviewed by themselves and relevant members of the trial team before dissemination of the results
- The final report is provided to the regulatory bodies in accordance with the timeline listed below:

- For CTIMPs with a paediatric population – within 6 months of the end of trial date
- For any trials in adult only population – within 12 months of the end of trial date

7.6.1. End of Trial Final Report to REC

The CI or delegate will:

- Prepare the End of Trial Final Report
- For trial submitted via combined review, the final report form is completed and submitted via IRAS
- For trials not submitted via combine review, the final report is submitted to REC using the webform available on the HRA website

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/final-report-form/

  - The Final Report webform must be completed online in one entry as it is not possible to save partially completed information and return to it at a later point. There is guidance next to each question of the form
  - Report questions can be copied and pasted from the website and added to a word document in order that responses to questions can be edited and reviewed by the trial team before online submission

- Upon submission of the End of Trial Final Report to REC, file acknowledgement of receipt and a copy of the final report in the relevant section of the TMF. This will be the PDF of the Final Report downloaded from the new part of IRAS for combined review trials or the automated REC email confirming that the Final Report has been received via the webform. This will contain a copy of all the information submitted in the webform for non-combined review trials
- Provide copy of the REC Final Report, and REC acknowledgement of receipt to:
  - The Regulatory Team for inclusion in the Sponsor File
  - Participating sites for inclusion in the ISF

7.6.2. End of Trial summary results and notification to MHRA

- Refer to CCTU/GD059 Registering Clinical Trials
- Ensure a full dataset is finalised and ready for posting within 12 months (or 6 months for Paediatric trials) following the conclusion of the trial
- Upload the full dataset as required to the appropriate Clinical Trial Registry

7.6.3. Publish Summary of Results Clinical Trial Registry

- Once data has been successfully uploaded and the results become public,
- The CI or delegate will send a short confirmatory email to the MHRA stating "End of trial: result-related information: IRAS ID XXXXX" in the subject line. The summary of results does not also need to be provided with this notification

The datasets posted and confirmatory email to the MHRA along with their acknowledgment email will be filed by the CTC/coordinating team in the TMF and provided to:

- The CCTU Regulatory team for inclusion in the Sponsor File
- The Participating sites for inclusion in theISF

7.6.4. Report to Funder(s)

The trial funder will be notified of the end of trial and sent the end of trial final report; some funders will request the end of trial final report on their own template (provided to CI via a portal)

7.7. Sponsors End of Trial Confirmation Letter

- Once all outstanding regulatory reporting requirements are completed and any closeout visit findings have been rectified, the Clinical Trials Officer will send the trial team the Sponsors end of trial confirmation letter using the template in ReDA
- The Sponsors end of trial confirmation letter signifies the end of all close out activities, regulatory reporting activities and triggers the archiving process
- The end of trial confirmation letter will detail the following information:
  - Archiving requirements
  - Publications, Abstracts and Presentation requirements
  - Any other relevant information specific to the trial

7.8. Participating Site Closing Letter

- Once all participating site closeout activities have been completed, the Sponsor will confirm with the trial team that the Participating Site Closing Letter (CCTU/TPL101) can be sent to the site(s). The Participating Site Closing Letter will give permission to sites to archive site files and pharmacy files, and the following will also be provided with the letter:
  - Archiving Form (CCTU/FRM017) for ISF/PF
  - End of Trial Final Report that was submitted to the REC
  - The clinical trial registry summary of results
  - Investigator Site File Index for Archiving TPL033 (Optional)
  - Pharmacy File Index for Archiving TPL038 (Optional)
- In certain circumstances (such as no patient recruitment or completion of all patients at the site significantly earlier than trial closure), participating sites may be permitted to close prior to completion and submission of the End of Trial Report and clinical trial registry summary of results
- The letter will instruct sites to file the End of Trial report and published clinical trial registry summary of results in the archived files when finalised. This should be discussed with the Regulatory Team to determine if this is an appropriate course of action for the site/trial

7.9. Financial Reconciliation

Before the grant closes, all invoices to sites, suppliers, labs etc. must be paid.

Funders expect a final finance report FSTOX to be prepared with the help of the CUH and UoC finance departments.

7.10. Trial Publications

- Prior to dissemination of results to regulatory authorities, public registries, or other publications the CI and CTC, where required, must have reviewed the trial results
- At the request of the Research Compliance Committee, the Sponsor will review any publication prior to submission and all reasonable comments from the Sponsor will be incorporated prior to publication
- The CI is responsible for ensuring that any serious breaches, temporary halts or other significant incidents are accurately and transparently reported in the trial publication as required by the UK legislation
- The publication & dissemination process detailed in the protocol and IRAS form needs to be complied with
- The CI should refer to the funding contract where appropriate to ensure that they comply with the terms and conditions of the report publication clauses
- For any publication or dissemination of clinical trials and clinical research follow the guidance given by the Consolidated Standards of Reporting Trials (CONSORT), http://www.consort-statement.org/consort-2010
- All publications should be sent to the CCTU inbox cuh.cctu@nhs.net and a copy placed in the TMF and retained centrally in the CCTU

7.11. Archiving

- The trial can be archived when the Sponsors End of Trial Confirmation Letter has been received
- 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 CCTU/SOP006 The CCTU Archiving Process

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.

MHRA, Good Clinical Practice "Grey Guide"

Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012XC1006(01)&from=EN

10. Associated Documents

CCTU/SOP006 The CCTU Archiving Process

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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