Standard Operating Procedure CCTU/SOP004

End of Trial Procedures

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 covers the end of trial or early termination declarations, site closure, end of trial reports, publications, and outlines the process to ensure that 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, GCP and applicable regulatory requirements.

It is integral to the quality assurance of clinical trials to ensure the integrity of the documentation 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.

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 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
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 (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 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 which 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 which 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 which 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 which 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
CTIMP	Clinical Trial Investigational Medicinal Product
EPIC	Electronic Patient Record
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PS	Participating Site
ReDA	Research Data Base Application
REC	Research Ethics Committee
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:
    - The CI submits the completed end of trial declaration form directly to REC
    - The CI submits the completed end of trial declaration form to the CCTU regulatory team, who will make submission to MHRA on behalf of the Sponsor
- Ensuring the provision of documentation for the Investigator Site File at all participating sites in the trial
- Completing analysis of trial data and generating the end of trial report/dataset within the regulatory timeframe from the date the trial concluded as recorded on the end of trial declaration
- Archiving of the TMFs (including the Pharmacy file and TMF Site Information files) following CCTU close out visit
- 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 fully and appropriately
- Managing the research samples long term storage or destruction according to details stated in the IRAS application

The CCTU is responsible for:

- Obtaining all end of trial documentation and updating the trial tracking tools
- Making the submission to MHRA on behalf of the Sponsor
- The close-out visit at Cambridge University Hospitals NHS Foundation Trust 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

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/TPL069 Close-Out Monitoring Report

CCTU/TPL037 End of Trial Report Template

CCTU/GD008 Monitoring Activities Guidance Document

CCTU/TPL061 Remote Monitoring Report Template

CCTU/SOP044 Research Sample Management

CCTU/FRM097 Hard Lock Completion Confirmation

6. Summary of Significant Changes

The CCTU no longer need to review the dataset before publication

Clarifications on requirements for database locking and the final close out visit
Additional information provided on regulatory reporting for multi-national trials

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 to 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 the both 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.
- The Chief Investigator (CI) or delegate will complete the Declaration of End of Trial Form available from the MHRA website at:
  https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial
- The Declaration of End of Trial Form must be reviewed by the Regulatory Team prior to signature and submission to any regulatory agency/ethics committee

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:

- The CI or delegate will:
  - Submit the notification 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 and R&D:

- The CCTU will:
  - Submit the notification 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 CI or delegate for inclusion in the TMF

- The CCTU will provide confirmation to the R&D department once the end of trial declarations have been submitted

Notification to Participating Sites & Other Organisations:

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

7.2. Participating Site Closure

- The Participating Site may only be closed when all data queries have been answered, resolved and documentation returned to the coordinating team as necessary
- Once all required 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:
    - Telephone conference, or
    - Remote monitoring
        - The coordinating team will distribute CCTU/TPL061 to participating sites for completion. Upon receipt, Participating sites are expected to complete and return the completed form in advance of site closure
    - On-site visit
        - CCTU/TPL069 should be completed for all site close-out visits
- 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
    - Discrepancies in the ISF documentation and arrangements for resolution
    - 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. Cambridge University Hospitals NHS Foundation Trust Site Closure

- The PI at Addenbrooke's is responsible for ensuring that all patients registered in EPIC and linked to the trial are marked as completed/withdrawn prior to the close-out visit
- 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
    - 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
- A single final close out visit report will be completed*
- Close-out visits will be conducted by Clinical Trials Monitors, where this is delegated or contracted out to external organisations/monitors, CCTU will maintain oversight by reviewing completed close-out report prepared by external/contract monitor.*
- For trials closed to the MHRA but remain open to REC, such as trials with long term follow up beyond active phase, monitoring will continue on reduced frequency and close-out visit should only be completed when the trial is closed to REC.

The Clinical Trials Monitors 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 documentation is present
- Request any outstanding documentation for the sponsor file during the close-out visit
    - Ensure that the final non-compliance log is printed and signed by the CI at the final close out visit
- Complete the Close-Out Monitoring Report CCTU/TPL069 and follow review process detailed in CCTU/SOP011
- Send a close-out visit follow-up letter to the Chief Investigator
- File a copy of fully signed report and follow up letter in the Sponsor File and the TMF

The CCTU Operations Director or Designee will:

- Review the report and feedback any comments or actions to the Sponsor
- Sign the completed final copy of the visit report

7.4. Outstanding Actions

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

7.5. Sample Handling

- The CI is responsible for ensuring research samples are stored or destroyed according to the requirements stipulated in the clinical trial protocol and IRAS form one year from the conclusion of the trial. Refer to CCTU/SOP044 Sample Management

7.6. End of Trial Reporting

- The CI will confirm that they are satisfied with the trial database locking process by completing and signing CCTU/FRM097 Hard Lock Completion Confirmation form.
- Documented evidence that the reported trial data is based on the final statistical report must be filed in the TMF together with the completed and signed CCTU/FRM097It is the CI's responsibility to ensure analysis is completed and the summary report is provided to the regulatory bodies in accordance to 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

End of trial Report to REC:

- The CI or delegate will:
- Prepare the end of trial report using the End of Trial Report Template CCTU/TPL037 and the GCP guidance document "structure and content of clinical study reports" (CPMP/ICH/137/95) available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002832.pdf
- As a minimum the end of trial report must contain the following information:
    - 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 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
    - Populations analysis
    - The main findings of the trial
    - A listing of all the significant non-compliances that occurred during the trial and how these contributed to the analysis
    - Details of any serious breaches reported during the trial
    - Arrangements for publication
    - Dissemination of the research including feedback to participants
- The CI or delegate will provide the End of Trial Report to the CCTU for review
- Upon review, the CCTU reviewer will confirm Sponsor's permission to the coordinating team to submit to REC
- The CI or delegate will:

- Submit the End of Trial Report to REC, file submission email and subsequent acknowledgement of receipt in the relevant section of the TMF
- Provide copy of the final report submitted, submission email and acknowledgement of receipt to:
  - The CCTU for inclusion in the Sponsor File
  - Provide documents to participating sites for inclusion in the ISF

End of Trial summary results to MHRA – publication of full dataset on EudraCT:

(In lieu of submitting of End of Trial Report, including all trials completed/terminated early after 21 Jul 2014)

- The CI will ensure full dataset is finalised and ready for posting within 12 months (or 6 months for Paediatric trial) following the conclusion of a clinical trial.
- The CI or delegate will upload the full dataset as required by EudraCT:
  - In order to report results via EudraCT, the user must be registered with the system as a results reporter
  - Results data can be directly entered into the system using the fields provided or uploaded via an .xml file
- Once data has been successfully uploaded, the CI or delegate will send a short confirmatory email to CT.Submission@mhra.gsi.gov.uk, stating "End of trial study report: EudraCT XXXX-XXXXXX-XX" in the subject line
- The datasets posted with confirmatory email will be filed in relevant sections of:
  - The TMF by the coordinating team
  - The Sponsor File by the CCTU Regulatory team
  - The Participating Site's ISF as provided by the Coordinating team
- NOTE: Failure to report results via EudraCT within the required timelines can adversely affect future regulatory approvals for the Sponsor

7.7. End of Trial Confirmation Letter

- The end of trial confirmation letter signifies the end of all close out activities, regulatory reporting activities and triggers the archiving process
- Once all outstanding regulatory reporting requirements have been completed and any close-out visit findings have been rectified, the Clinical Trials Officer will send the trial team an end of trial confirmation letter using the template in ReDA
- 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. Trial Publications

- 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 publication policy should be detailed in the protocol and IRAS form submitted to REC
- The CI should refer to the funding contract where appropriate to ensure that they comply with the terms and conditions of the report publication policy.
- 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 with a copy placed in the TMF and Sponsor File

7.9. Archiving

- The trial can be archived when all the end of trial documentation and end of trial reports have been written, submitted and filed
- 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 http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

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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