Standard Operating Procedure CCTU/SOP014

Amendment Management of CTIMPs by Trial Teams

1. Scope

This SOP applies to all trial teams running Cambridge Sponsored clinical trials of investigational medicinal products (CTIMPs).

This SOP does not apply to commercially sponsored trials or CTIMPs sponsored by an external non-commercial organisation.

2. Purpose

To ensure that all planned amendments for sponsored CTIMPs are appropriate and do not have any impact on the Trust/University of Cambridge's agreement to continue sponsorship of the 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); jointly by CUH and the University of Cambridge (UoC); OR Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Substantial Amendment	Amendment to Clinical Trial/REC application, the protocol or any other supporting documentation, that is likely to affect to a significant degree: -The safety or physical or mental integrity of the subjects of the trial -The scientific value of the trial -The conduct or management of the trial -The quality or safety of any investigational medicinal product used in the trial
Non substantial Amendment (Minor)	Amendments made to any of the trial documentation including the application forms, protocol or supporting documentation which do not fall into the categories above
Trial Team	Includes the Chief Investigator (CI), Principal Investigator (PI), Clinical Trials Coordinator (CTC), Data Manager (DM), trial Statistician, Database Programmer, Research Nurse as identified and delegated by the CI and/or Sponsor at the Coordinating Centre/Lead Site.

3.2. Abbreviations

Abbreviation	Meaning
ARSAC	Administration of Radioactive Substances Advisory Committee
C&C	Capability and Capacity
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CPFT	Cambridgeshire & Peterborough NHS Foundation Trust
CRN	Comprehensive Research Network
CRF	Case Report Form
CTC	Clinical Trials Coordinator
CTIMP	Clinical Trials of Investigational Medicinal Product
CTO	Clinical Trials Officer
CUH	Cambridge University Hospitals NHS Foundation Trust
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines & Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
TMF	Trial Master File
TSC	Trial Steering Committee
UoC	University of Cambridge

4. Undertaken by

The Chief Investigator (CI) and Principal Investigator (PI) or delegated trial team conducting Trust Sponsored clinical trials.

The CCTU Regulatory team:

- Has been delegated the responsibility for classification of amendments by the Sponsor
- Is responsible for submitting substantial amendments to the MHRA

5. Items Required

CCTU/SOP019 Urgent Safety Measures

Amendment Tool & Annex 2 Form

6. Summary of Significant Changes

The addition of pre-approval/notification of the amendment to CUH/CPFT Legal, Funder and TSC

Change of responsibilities for obtaining lead site C&C Confirmation and onward notification to lead site support departments and Insurance Office

7. Method

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

7.1. Responsibilities

It is the trial teams' responsibility to:

- Ensure the amendment has been discussed with and agreement received from the Funder, TSC/DMC and relevant legal team as appropriate where resource implications are identified
- Prepare all amendment documentation for submission to the CCTU regulatory team for review prior to submission
- Notify and submit amendments to relevant parties (e.g. insurance provider, pharmacy, laboratories) in a timely manner
- Ensure that relevant documentation and pertinent correspondence relating to all amendments is filed in the TMF
- Ensure that all participating sites are notified of the amendment in a timely manner
- Consider whether the amendment will have any impact on the CRF and database and to contact the Data Management/Programming team(s) accordingly
- Submit amendments to the REC/HRA/ARSAC after Sponsor Authorisation to submit has been granted
- Provide training to local trial teams prior to amendment implementation as required

7.2. Amendment Requirements

The HRA and MHRA websites provide specific guidance for the management of amendments

The Amendment Tool and associated Annex 2 form where appropriate, are available from the HRA website and must be completed for all amendments.

7.2.1. Substantial Amendments

Substantial amendments must receive approval from the REC and/or the MHRA, HRA and R&D (C&C) prior to implementation except when Urgent Safety Measures need to be implemented. Refer to CCTU/SOP019 Urgent Safety Measures for further details

7.2.2. Non-substantial Amendments

- Sponsor authorisation must be granted prior to submission of non-substantial amendments to the HRA
- Non-substantial amendments must be acknowledged by the HRA prior to implementation. They do not need to be notified to the REC or MHRA

7.3. Preparation of Amendment Documentation

- Depending on the nature of the proposed amendment it may be necessary to obtain input from relevant departments/study personnel (e.g. pharmacy, labs, study statistician, radiology etc.)
    - Amendments which have an impact on resources and contracts must be discussed with the relevant legal team prior to submission to the CCTU Regulatory Team
- The trial team should ensure that all study documents affected by the amendment are updated. For example, an amendment to the protocol may require an update to the participant information documents, IRAS application form and CRFs
- If the amendment has an impact on the CRF and database (e.g. changes to participant assessments, visits, samples or inclusion/exclusion criteria) the Data Management/Programming team(s) should be contacted as early in the amendment process as possible to ensure that the systems are updated and available for implementation following amendment approval
- A substantial amendment should include all updated trial documents with tracked changes, the completed Amendment Tool and Annex 2 (if applicable) and covering letter(s)
    - For complex substantial amendments, a Summary of Changes document may also be appropriate
- A non-substantial amendment should include all updated trial documents with tracked changes, the Amendment Tool and a covering letter/email

7.4. Submission of Amendments for Authorisation from CCTU

Both substantial and non-substantial amendments should be submitted by the trial team to the CCTU regulatory team via ccturegulatory@addenbrookes.nhs.uk for review and authorisation prior to submission to relevant regulatory authorities

- Note, any changes required by the regulatory bodies during the review process, must be reviewed and authorised by the CTO prior to re-submission

7.5. CCTU Amendment Review & Authorisation

- The CTO will check that all required documentation has been submitted for review and request any outstanding documentation prior to starting the review process
- Any suggested or required changes to the documentation will be provided to the trial team using the tracked changes mode wherever possible to allow quick review and agreement of the changes
- The CTO will complete the review process normally within 3 working days of receiving the final documents
- Only the CTO is permitted to authorise the Amendment Tool
    - The CTO will authorise the Amendment Tool and return a PDF 'locked' copy to the trial team for submission.

The CTO will send an email to the trial team confirming Sponsor Authorisation for submission of the amendment and supporting documentation to the reviewing bodies (REC/HRA and/or MHRA)

7.6. Submission to Regulatory Bodies (MHRA/REC/HRA)

Specific guidance on the format and content of amendment submissions can be found on the HRA and MHRA websites

The Regulatory Team must be notified once amendment submissions have been made to the REC/HRA

- All amendments should be submitted as soon as possible after sponsor authorisation from the CCTU regulatory team, normally within 10 working days. Any significant delays in submissions to the regulatory bodies should be notified to the CCTU regulatory team
    - Where significant delays are experienced, re-authorisation of the amendment may be required. Please check with the CTO
- Submissions to the MHRA will be made by the CTO upon receipt of final signed PDF documents. Copies of the submission documentation and emails will be provided to the trial team for filing in the TMF
- The trial team must provide a copy of all communications with the regulatory bodies to the CTO

7.7. Submission to Other Regulatory Bodies

For studies being conducted in sites outside the UK

- Substantial amendments are submitted to the Ethics Committee and/or relevant Competent Authority according to local country requirements by the trial team or local country lead delegate as soon after possible after authorisation from the CCTU regulatory team, normally within 10 working days
- Amendment submissions to ARSAC or other equivalent regulatory bodies must be made by the trial team following the process described in 7.6.
- Any significant delays in submissions to these bodies should be notified to the CCTU regulatory team
- A copy of the submitted documents and approvals should be filed in the TMF/ISF

7.8. Receipt of Regulatory Body Acknowledgements & Approvals

- Written confirmation will be provided to acknowledge and/or approve or reject the amendment by all regulatory bodies
    - Please note: any changes requested by the regulatory authorities to the trial documents must be reviewed and re-authorised by the CTO prior to re-submission
- The outcome of ethical review will be provided directly to HRA by the REC
- The MHRA do not share the outcome of their review with the HRA. The trial team must send a copy of the MHRA amendment acceptance to the HRA as soon as it is available to avoid delays with HRA approval

- All relevant documentation (including acknowledgments, approvals and pertinent correspondence) relating to the amendment must filed in the TMF and a copy provided to the Regulatory Team for the Sponsor File

7.9. Notification to Lead and Participating Sites

- The trial team is responsible for disseminating the amendment package to:
  - Local research teams and R&D offices of the lead site
  - Local research teams and R&D offices of participating sites
  - The CRNs
- REC/HRA/MHRA approval letters must be forwarded to the lead and participating site research teams and R&D departments as soon as possible after receipt to ensure timely approval/implementation of the amendment
- The trial team must file the lead and participating site C&C confirmation letters/emails (if provided) in the TMF
  - Note: Some R&D Departments do not issue continuing C&C letters or emails as per their local policy. This should be noted, per site, in the TMF

7.10. Notification to Supporting Departments at Lead Site

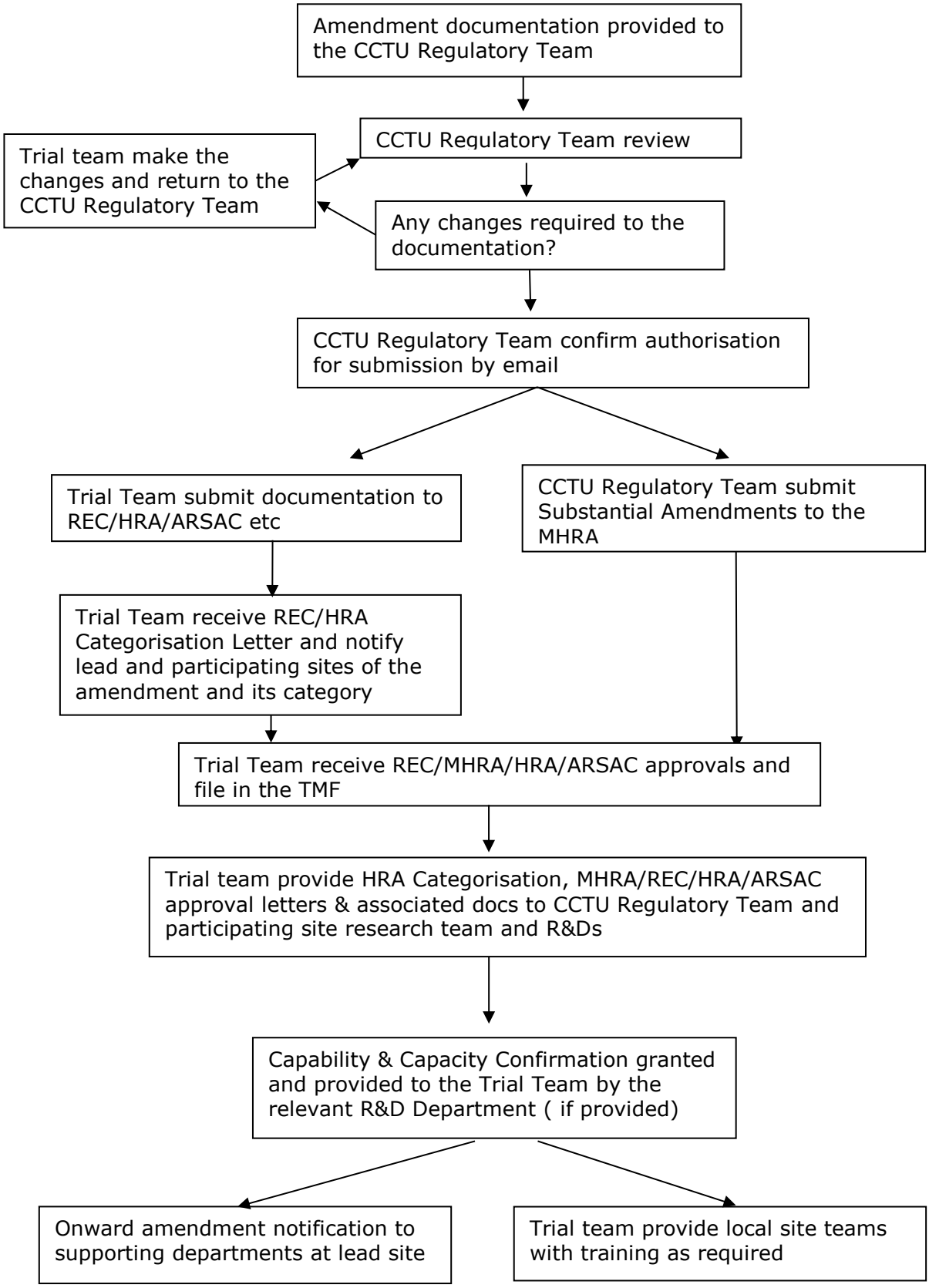
- It is the responsibility of the trial team to ensure that all amendment documentation including regulatory body and local CUH/CPFT C&C Confirmation are provided to the supporting departments where appropriate
- This includes, but is not limited to;
  - Pharmacy
  - UoC Insurance Office (if jointly sponsored)
  - Local and central laboratories
  - Cambridge Clinical Research Centre (CRF/CIW)
  - Data Management/Programming team
  - Funding bodies
  - Randomisation system manager

7.11. Amendment Implementation

- All amended protocols should be signed and dated (wet ink signature) by the CI and filed in the TMF
- Where substantial amendments which include significant changes to the:
  - Trial assessments
  - Patient visits
  - Trial processes
  - IMP handling/dispensing
- Participating site teams undertaking these responsibilities will require central training (provided by the trial team)
- Participating sites must be made aware that there is an expectation that training must be completion prior to implementing the amendment

- The requirements, content, delivery method and documentation of the training should be discussed with the CTO as part of the ongoing trial risk assessment process

7.12. Amendment Flow Chart



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"

European Commission, 2010, 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 trial (CT-1)

For further information and guidance on submissions and review timelines, please see the HRA website: https://www.hra.nhs.uk , and the MHRA website: www.mhra.gov.uk and amendments help section in the Integrated Research Application System (IRAS) IRAS

10. Associated Documents

None

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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