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 research 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. To clarify the responsibilities of the Sponsor, the CCTU and the Trial team

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
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
Minor/non substantial Amendment	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
C&C	Capability and Capacity
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
LCRN	Local Comprehensive Research Network
CESP	Common European Submission Portal
CRF	Case Report Form
CTIMP	Clinical Trials of Investigational Medicinal Product
CTO	Clinical Trials Officer
CUH	Cambridge University Hospitals NHS Foundation Trust
GCP	Good Clinical Practice
HRA (and HCRW)	Health Research Authority (& Health and Care Research Wales)
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
UoC	University of Cambridge

4. Undertaken by

Chief Investigators (CI) and Principal Investigators (PI) or their trial team as delegated within the Trust conducting Trust sponsored clinical trials.

Classification of amendments is the responsibility of the Sponsor. This has been delegated to the CCTU Regulatory team.

The CCTU regulatory team is responsible for submitting substantial amendments to the MHRA using the CESP portal

5. Items Required

CCTU/SOP019 Urgent Safety Measures

IRAS Amendment Form (from the Amendments tab for your trial in IRAS)

HRA Notification of non-substantial/minor amendments form

6. Summary of Significant Changes

Update to local C&C approval process and notification to supporting departments, and re-structure of entire document for clarity.

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 CI or trial teams' responsibility to:
- Prepare all amendment documentation for submission to the CCTU regulatory team for review prior to submission.
- The CCTU regulatory team is responsible for submitting substantial amendments to the MHRA using the CESP portal
- The CI/trial team must also:
- Notify and submit amendments to relevant parties (e.g. insurance provider, pharmacy, Trial Steering Committee, Data Monitoring Committee and /or funder(s)) 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 team accordingly
- Submit amendments to the REC/HRA after Sponsor Authorisation to submit has been granted (unless otherwise agreed)

7.2. Amendment Requirements

- The HRA and MHRA websites provide specific guidance for the management of substantial amendments
- If you are unsure whether the amendment is a minor or substantial amendment, or which documents you need to complete/update please contact the CCTU regulatory team for further guidance

7.2.1. Substantial Amendments

- Substantial amendments must receive approval from the REC and/or MHRA and/or HRA and R&D (or sponsor representative) prior to implementation except when Urgent Safety Measures need to be implemented. Refer to CCTU/SOP019 Urgent Safety Measures for further details
- Substantial amendment forms must be generated on-line via the Amendments tab in IRAS then appropriately signed and submitted according to the REC/HRA & MHRA requirements

7.2.2. Minor/Non-substantial Amendments

- Minor/ Non-substantial amendments must be approved by the HRA (and HRCW) prior to implementation. They do not need to be notified to the REC or MHRA
- Sponsor authorisation must be granted prior to submission of minor amendments to the HRA

- Minor amendments must be accompanied by a non-substantial amendment form which can be downloaded from the HRA website
- Capability and Capacity Confirmation is not required for non-substantial amendments however R&D will be informed by the assigned CTO handling the amendment

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.)
- The CI or 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, clinical trial 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 team should be contacted as early in the amendment process as possible to ensure that these systems are updated and available for implementation following the amendment approval
- A substantial amendment should include all updated trial documents with tracked changes, the completed Notice of Substantial Amendment form and covering letter(s)
- A non-substantial amendment should include all updated trial documents with tracked changes, the completed Non-substantial Amendment Form and a covering letter/email
- Depending on the nature of the amendment it may also be necessary to include an additional document which summarises the changes, for example, extensive protocol changes

7.4. Submission of Amendments for Authorisation from CCTU

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

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
- As part of the review process, the CTO will confirm whether the amendment is substantial or minor
- Any suggested or required changes to layout or wording of the documentation will be provided to the CI or trial team using the tracked changes mode 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
- The CTO will send an email to the CI or 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
- Substantial amendments that require REC review are submitted by email to the REC that originally reviewed the trial documentation
    - If the REC is in England, the amendment package should be e-mailed to the REC only (they will share with the HRA amendments team)
    - If the REC is in Northern Ireland, Scotland or Wales AND the lead NHS R&D office is in England, the amendment package should be e-mailed to REC and copied to hra.amendments@nhs.net
- Minor amendments should only be submitted to the HRA via email to hra.amendments@nhs.net
- All amendments should be submitted as soon as possible after 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
- Amendment submissions to the MHRA will be made by the CTO via CESP. Copies of the submission documentation and emails will be provided to the trial team for filing in the TMF
- For submission of substantial amendments to the REC the documentation should also include the Sponsor Authorisation email
- The REC and MHRA have 35 days from acknowledgement/validation to review the amendment and the HRA also have the aim of reviewing the amendment within this time period
- The REC validation letter will confirm the documents received, including dates and version numbers – these should be checked as the approval will be based on the information contained in this letter
- The MHRA acknowledgment letter will confirm receipt of the amendment and state the 35 day timeline for review
- The CI or trial team should provide a copy of the final submitted documents including clean versions of the amended trial documentation to the CTO

7.7. Submission to Other Regulatory Bodies

- For studies being conducted in sites outside of the UK all substantial amendments should be 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

- Any significant delays in submissions to these bodies should be notified to the CCTU regulatory team
- In most cases written confirmation will be provided to approve or reject the amendment by regulatory bodies
- A copy of the submitted documents and approvals should be filed in the TMF/ISF

7.8. Receipt of Regulatory Body Categorisation/Approvals

- Written confirmation will be provided to approve or reject the amendment by all regulatory bodies
- The HRA Amendment Assessment Team should categorise all amendments according to the UK amendments process and inform the applicant of the outcome within 5 days via e-mail.
- The categorisation e-mail will confirm the category of the amendment
    - A (all sites to consider)
    - B (specified sites to consider)
    - C (sites not expected to consider)
    - New site (addition of new site/change of PI at existing site), arrangements for handling the amendment with the participating sites and whether further HRA assessment of the amendment is required
- The outcome of ethical review will be provided directly to HRA by the REC
- The MHRA will not share the outcome of their review of the amendment with the HRA. The CI/trial team should send a copy of the MHRA acceptance of the amendment to the HRA as soon as it is available
- Upon receipt of the HRA/REC categorisation e-mail and/or REC/HRA/MHRA acknowledgment and approval letters, copies should be forwarded to the CTO as soon as possible
- Where appropriate, local CUH Capability & Capacity Confirmation for the amendment will be forwarded to the trial team by the CTO/Research Governance Co-ordinator
- The CI/trial team must provide a copy of the local CUH C&C confirmation/Sponsor approval to the data management team to ensure that any amendments to the CRF and database can be released for use
- All relevant documentation (including acknowledgments, approvals and pertinent correspondence) relating to the amendment must filed in the TMF

7.9. Notification to Participating Sites

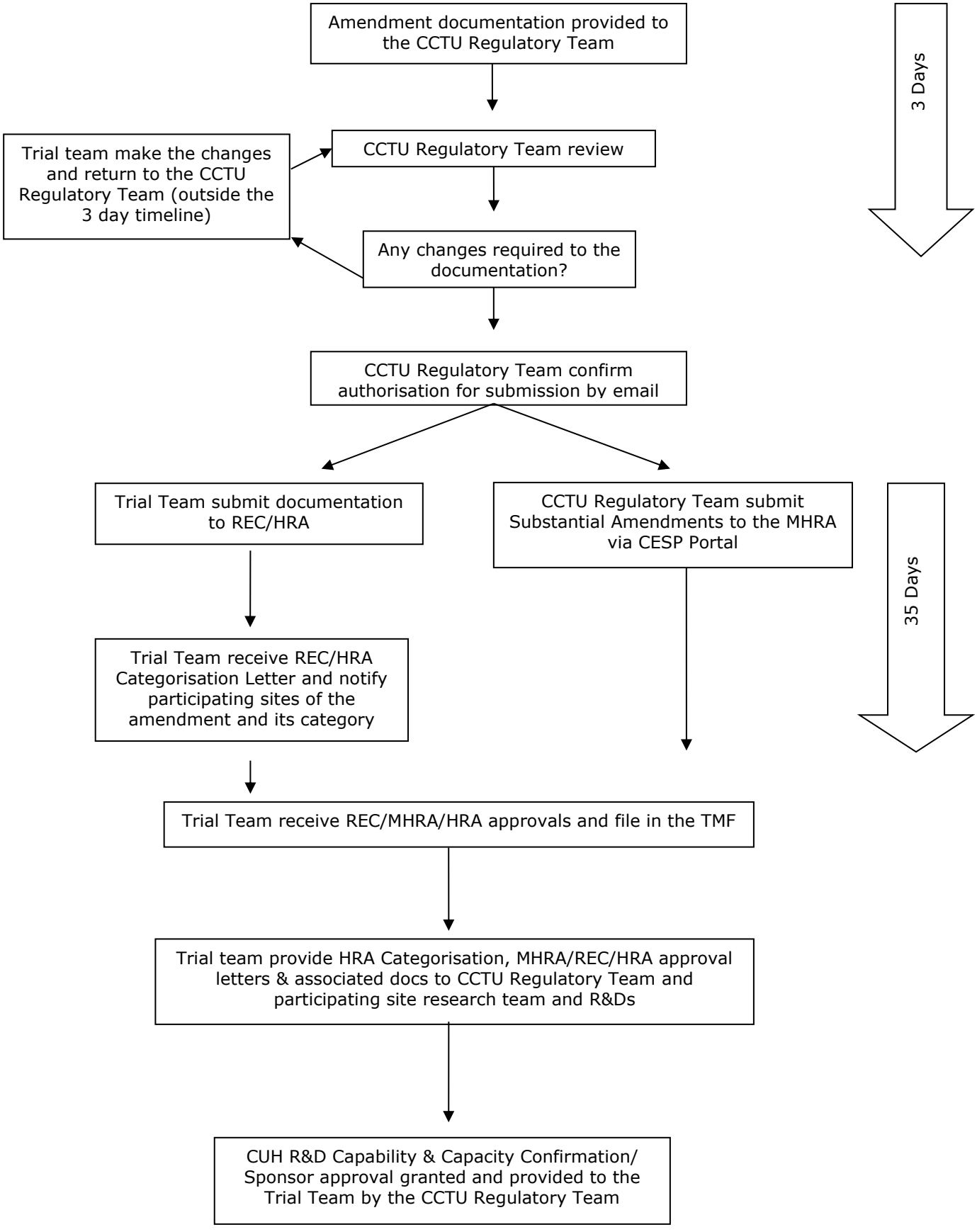
- For substantial amendments, the trial team is responsible for disseminating the amendment package and categorisation e-mails to local research teams and R&D offices of the participating sites and for ensuring that the LCRNs are also informed
- This should happen as soon as the HRA/REC categorisation e-mail is received but within 10 working days

- For minor amendments the trial team will provide the R&D department at each participating site with the amendment documents as soon as possible, normally within 10 working days, after HRA approval has been received
- REC/HRA/MHRA approval letters are forwarded to the participating site research teams, R&D departments and LCRNs as soon as possible after receipt to ensure timely approval of the amendment
- The trial team must file the participating site R&D acknowledgment letters/emails in the TMF

7.10. Notification to Supporting Departments

- It is the responsibility of the trial team to ensure that all amendment documentation including regulatory body and local CUH Capability and Capacity Confirmation are provided to the supporting departments where appropriate
- This includes, but is not limited to;
    - Local and central laboratories
    - Clinical Research Facilities (CRF) or Clinical Investigational Wards (CIW)
    - Data Management team
    - Funding bodies
    - Randomisation system manager

7.11. 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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