

Standard Operating Procedure CCTU/SOP014

Modification 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 modifications 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 Modification	<p>The term 'amendment' has been replaced with 'modification' with the introduction of Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538.</p> <p>Substantial modifications can be categorised as Route A or Route B:</p> <p>Substantial modifications via Route A are changes that have a substantial impact on the safety or rights of the participants or on the reliability or robustness of the data generated in the trial.</p> <p>Substantial modifications via Route B are changes that do not introduce new significant safety concerns or risk and that fit within the defined, strict criteria defined in regulation 11B of the Clinical Trial Regulations 2025.</p> <p>As a result of the lower risk change criteria in a Route B substantial modification, Route B modifications have a streamlined, faster MHRA regulatory pathway to approval compared to Route A. However, if review by the REC is also required the review timelines will remain the same as Route A.</p>

Modifications of an Important Detail	Modifications that do not significantly impact the safety or rights of the participants, but the authorities need to be aware of them for administrative or oversight purposes. Instructions for notifying the authorities about a modification of an important detail are provided upon completion of the Modification Tool.
Minor Modifications	Minor modifications may be implemented at any time and without informing the licensing authority (MHRA) or ethics committee at the point of implementation. However, other approvals may be required, which can be determined using the Modification Tool. Records must be kept of all minor modifications implemented and, if requested, be made available to the licensing authority or ethics committee.
Participating Site	Referred to in the regulations as a 'Trial Location' currently defined as: a hospital, health centre, surgery or wider healthcare setting, or facility or premises at or from which a clinical trial, or any part of such a trial, is conducted. For the purposes of CCTU SOPs, Forms and Templates, this does not include Participants homes.
Request for Further Information	The MHRA and REC can request further information when considering substantial modification requests. This means that, if the MHRA or REC identify issues that prevent a substantial modification request from being approved, the trial team will be informed of these issues and will be able to respond before a final decision or opinion is issued.
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 Participating Site.

3.2. Abbreviations

Abbreviation	Meaning
ARSAC	Administration of Radioactive Substances Advisory Committee
C&C	Capability and Capacity
CI	Chief Investigator
CRN	Clinical Research Network
CRF	Case Report Form
CRS	Combined Review Service
CTC	Clinical Trials Coordinator
CTIMP	Clinical Trials of Investigational Medicinal Product
CTO	Clinical Trials Officer
DMC	Data Monitoring Committee
HRA	Health Research Authority
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines & Healthcare products Regulatory Agency
MOID	Modification of an Important Detail

PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
RFI	Request for Further Information
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 modifications by the Sponsor
- Is responsible for submitting substantial modifications (Route A and B) to the MHRA for CTIMPS not originally submitted through the combined review (CRS) process

5. Items Required

- CCTU/SOP019 Urgent Safety Measures
- Modification Tool
- CCTU/TPL094 Modification Impact Form Template

6. Summary of Significant Changes

Widespread changes in response to the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538

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 modification has been discussed with and agreement received from the Funder, TSC/DMC and relevant legal team as appropriate where resource implications are identified
- Prepare modified documents that need review by the Regulatory Team prior to submission and email to Regulatory Team as tracked, editable (e.g. MS Word) versions
- Notify and submit modifications to relevant parties (e.g. insurance provider, pharmacy, laboratories) in a timely manner
- Ensure that relevant documentation and pertinent correspondence relating to all modifications are filed in the TMF

- The trial coordinator/delegate will consider whether the modification will have an impact on any other trial documentation, the IRAS form, CRFs, Database, Trial Manuals, Critical to Quality Factors and Risk Assessment, Monitoring Plan etc. as listed on CCTU/TPL094. The list will include both documents that need to be submitted to the CCTU Regulatory Team and subsequently REC and MHRA as well as other documentation that does not need to be submitted but is needed in order to run the trial
- The trial coordinator/delegate will discuss any required changes to other trial documentation or systems with the CI's team and other relevant members of the TMG (e.g. data managers, programmers, statisticians, pharmacist etc.)
- CCTU/TPL094 will be completed with details of all documents impacted by the modification and signed by coordinator/delegate
- Timelines for revisions of all documents impacted, including updates to the database and eCRF if appropriate, should be discussed and agreed before the modification is submitted
- Submit modifications to the review bodies following Sponsor Authorisation to submit
- Ensure that all participating sites are notified of the modification in a timely manner. The Modification Tool will provide the appropriate categorisation and guidance on communicating the modification to participating sites once submitted
- Provide other supporting trial documentation as identified in the Modification Impact Form (e.g. CRFs, manuals etc), to local trial teams prior to modification implementation as required
- Provide training to local trial teams prior to modification implementation, as required

7.2. Modification Requirements

The HRA, IRAS and MHRA websites provide specific guidance for the management of modifications

- Sponsor authorisation must be granted prior to submission of all modifications
- The Modification Tool is available as a resource from IRAS to assist in determining whether a modification needs to be reviewed by the MHRA, the ethics committee, or both.
 - The latest version of the Tool must be downloaded from the website for all new modifications to ensure categorisations are generated correctly
 - The Modification Tool Section 4 will provide additional guidance on how to submit the modification in IRAS (including the modification category to select in IRAS and whether IRAS forms also need to be updated), based on whether the trial was originally approved through combined review or not

7.2.1. Substantial Modifications

Substantial modifications must receive approval from the REC and/or the MHRA, the HRA and participating sites' 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

Substantial modifications are categorised as Route A or Route B

- Route A substantial modifications are considered likely to have a substantial impact on the safety or rights of the participants or on the reliability or robustness of the data generated in the trial
- Route B substantial modifications are changes that do not introduce new significant safety concerns/risk and that fit within the defined categories in [regulation 11B](#) of the Clinical Trial Regulations 2025. Specific criteria can be viewed in [Table 1: Route B substantial modifications](#), that is available on the MHRA website [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#)
 - Route B modifications are eligible for automatic, faster approval by the MHRA (note, if REC review is also required their timelines are not accelerated). There must be an explicit statement in the cover letter to confirm the modification is a Route B substantial modification and how it meets conditions for that
 - If there are a mix of Route A and B classified changes in a substantial modification it will be considered as Route A
- Route A and Route B substantial modifications must include in the cover letter an overview of the modification, with a clear justification / rationale for the changes. See, [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) for details of cover letter and other documentation requirements
- For CTIMPS NOT originally approved through combined review:
 - If the modification affects the information on the original Medicines Information form, an updated copy should be submitted (the form can be requested from clintrialhelpline@mhra.gov.uk for non-combined review trials)
 - The MHRA can be contacted for assistance in determining who needs to review the modification (and its type, Route A or B) at clintrialhelpline@mhra.gov.uk. See, [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#)
- A list of examples of Substantial Modifications (Route A and B) can be found on the HRA and MHRA websites with details.

7.2.2. Modifications of an Important Detail

- Modification of an Important Detail (MOID) changes are those that do not significantly impact the safety or rights of the participants, but the authorities need to be aware of them for administrative or oversight purposes
- Practical examples include: a change of investigator (PI) at a participating site, addition of a new site, or to notify the authorities of the date the trial's first participant was recruited alongside the date the public registry went live (a requirement for all new CTIMPS that have not recruited at the point the new regulations come into effect i.e. old rule and new rule trials)

- Instructions for notifying the authorities about a MOID are provided on completion of the Modification Tool (available on IRAS/HRA website)
- An acknowledgement email will be issued upon submission of a MOID, and there will be no approval email/letter
- A list of examples of MOIDs can be found on the MHRA and HRA websites
- There is no fee associated with placing MOIDs

7.2.3. Minor Modifications

- Minor Modifications are classified as modifications that do not fall under 'substantial modification' or 'modification of an important detail' such as administrative updates, logistical adjustments, small clarifications and similar non-critical changes
- Minor modifications can be implemented at any time without informing the MHRA and REC, although other approvals, for example HRA and HCRW Approval, may be required which can be determined using the Modification Tool
- If online submission of a minor modification is required, any system generated automated emails will be sent to the trial team. This should then be forwarded to the Regulatory Team via the CCTU regulatory email cuh.ccturegulatory@nhs.net
- Trial teams should follow the guidance in the Modification Tool on how to communicate the modification to participating site(s)
- All minor modifications (even if the Tool confirms an online submission is not required) must be documented and filed in the TMF, as they are still subject to review/inspection by the REC/Authorities
- A list of examples of minor modification can be found on the HRA website

7.3. Preparation of Modification Documentation

- Depending on the nature of the proposed modification it may be necessary to obtain input from relevant departments/study personnel (e.g. pharmacy, labs, study statistician, radiology etc.)
 - Modifications 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 modification are updated - see CCTU/TPL094. For example, a modification to the protocol may require an update to the participant information documents, CRFs & Trial Manuals and IRAS form.
- If the modification 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 modification process as possible to ensure that systems are updated and available for implementation following the modification approval
- All modification submissions should include all updated trial documents with tracked changes (including if changes are made to an IMPD or IB/SmPC), the completed Modification Tool and covering letter(s) (refer to [Clinical trials](#))

[for medicines: modifying a clinical trial approval - GOV.UK](#)) and a completed and signed CCTU/TPL094 Modification Impact form

7.3.1. Complex Modifications

- Complex modifications are those which significantly change the trial, such as the introduction of a sub-study or the addition of a new treatment arm
 - These modifications often require the same level of resource for review and implementation as a new trial and as such need to be carefully considered
- All complex modifications must be discussed with the CCTU Regulatory Team prior to submission of any modifications documents for review
- No additional changes, even MOIDS or minor modifications, will be permitted to be included with the complex modifications, due to the timelines associated with implementation at participating sites
 - Partial modification implementation is no longer permitted by the Sponsor

7.4. Submission of Modifications for Sponsor Authorisation

- The trial team must submit both substantial (Route A and B), modifications of an important details, and minor modifications to the CCTU Regulatory Team for review and authorisation prior to submission to the relevant regulatory authorities via the CCTU regulatory email cuh.ccturegulatory@nhs.net
- The completed, signed Modification Impact Form Template TPL094 should also be submitted to the Regulatory Team together with all modification documentation for all modification types
- 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. Sponsor 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
- For complex, extensive or wide-spread modifications (for example, the addition of a new IMP /arms, significant changes to the design etc) the CTO review process will be completed within 10 working days of receiving the final documents
- Only the CTO is permitted to authorise the Modification Tool
 - The CTO will authorise the Modification 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 modification and supporting documentation to the reviewing bodies (REC/HRA and/or MHRA)
- The CTO will also confirm if re-consenting of participants is required and / or if an update to the trial specific critical to quality factors and risk assessment is required

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

- Specific guidance on the format and content of modification submissions can be found on the IRAS, HRA and MHRA websites.

For CTIMPS approved through the combined review (CRS):

For CTIMPS originally submitted through combined review, the submission is a single modification package (including all [documentation](#)) made through CRS IRAS. The Regulatory Team must be notified when this has occurred so they can log in to the Sponsor CRS portal and approve the modification online, routing it to the regulatory bodies

For CTIMPs NOT approved through combined review (CRS):

For trials not originally submitted via the combined review service, submissions to the MHRA and REC/HRA will be made separately. The MHRA submission 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 will submit to the REC/HRA and the Regulatory Team must be notified once modification submissions have been made to the REC/HRA

- For all modifications Section 4 of the Modification Tool will provide guidance on which classification option to select in IRAS when completing the submission online to ensure the modification is processed correctly. This is provided because IRAS has not been updated in line with the regulations
- All modifications 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 modification may be required. Please check with the CTO
- The trial team must provide a copy of all communications with the regulatory bodies to the CCTU regulatory email, cuh.ccturegulatory@nhs.net
- Automated emails sent following successful submission online of a modification using the standard IRAS Identity Gateway or IRAS CRS are not automatically received by the Regulatory Team and should be forwarded to the CCTU regulatory email

7.7. Submission to Other Regulatory Bodies

For studies being conducted in participating sites outside the UK

- Substantial modifications 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
- Modification 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/validate the modification by all regulatory bodies
- Written confirmation of the outcome of the review will be provided, which can be either: Acceptance of the proposed modification; Approval of the proposed modification subject to conditions, or the authorises do not approve the proposed modification, setting out the grounds for this decision.
- For combined review trials, confirmation of outcomes for modification will also be available in the new IRAS
- 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 should send a copy of the MHRA modification acceptance to the HRA as soon as it is available to avoid delays with HRA approval (this applies to all CTIMPS, including combine review trials))
- All relevant documentation (including acknowledgments, approvals and pertinent correspondence) relating to all modifications must be 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 participating site
 - Local research teams and R&D offices of participating sites
 - The Clinical Research Networks
- Following online submission of a modification, trial teams should follow the guidance in the Modification Tool to communicate the modification to participating site(s)
- This will vary depending on location of participating site(s) and modification categorisation (A, B or C) and should be done as soon as possible upon submission to the review bodies in line with the Tool, unless the CTO advises otherwise (e.g. for complex modifications with widespread changes to trial management documents and database)

- 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 modification
- Other trial documentation that has been updated as part of the modification (e.g. eCRFs, database, manuals etc) should be sent to local trial teams prior to modification implementation
- Local trial teams are then responsible for the onward provision of modified documentation to other local support departments (e.g. laboratories, pharmacy, radiology etc)
- The trial team must also confirm as part of the notification to all participating sites whether re-consenting is required following the modification
- 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 according to their local policy
 - This should be recorded, per participating site, in the TMF

7.10. Notification to Supporting Departments at Sponsor Lead Participating Site

- It is the responsibility of the trial team to ensure that all modification 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)
 - Confirmation of continuation of cover from the UoC insurance office should be filed in the TMF and provided to the Regulatory Team for inclusion in the Sponsor File
 - Local and central laboratories
 - Cambridge Clinical Research Centre
 - Data Management/Programming team
 - Funding bodies
 - Randomisation system manager

7.11. Modification Implementation

- All amended protocols should be signed and dated (wet ink signature) by the CI & PIs and filed in the TMF
- Where substantial modifications which include significant changes to the:
 - Trial assessments
 - Participant 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 modification
- 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
- All documents impacted by the modification should be revised and ready for implementation by the time the modification has been approved. This includes the back-up pCRFs, worksheets, eCRFs, the database and any updated trial manuals or internal SOPs/process flows. These must be sent to participating site trial teams prior to implementation
- Any delays with modification implementation at any participating site (excluding complex modifications where timelines are expected to be lengthy) must be escalated to the CCTU Regulatory Team
 - As a priority details of the cause of the delay, actions taken and the timelines associated must be provided
 - This may require further escalation to the sponsor if delays persist
 - It may be necessary to halt the trial at a participating site if delays with modification implementation persist and it is likely to have an impact on participant safety or data integrity

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

Common Abbreviations and Definitions CCTU/INF001

Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538

For further information and guidance for submissions and the review timelines refer to:

- The HRA website: <https://www.hra.nhs.uk> ; [The approvals process for modifications \(amendments\) - Health Research Authority](#)
- The MHRA website: www.mhra.gov.uk ; [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#)

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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