Technology, Infrastructure and Environment Directorate Clinical Research Governance Team

Standard Operating Procedure

Procedure for the Submission of Modifications

SOP018

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1. Introduction

Modifications (previously called Amendments) are changes that are made to a research study after approvals have been issued for the study. This may be Sponsorship Approval, a favourable opinion from a Research Ethics Committee (REC) or approval from another regulatory body has been given. The modification can be made to a protocol, other essential documentation or other aspects of a study's arrangements.

This procedure details the process for submission and review of modifications and was written in accordance with The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, the UK Policy Framework for Health and Social Care Research, MHRA guidance and HRA guidance.

2. Scope of Procedure

This standard operating procedure (SOP) describes:

- The procedure for making modifications to the protocol, any other essential study documentation and/or the arrangements for the study/trial.
- The procedure for gaining the University of Liverpool (University) approval for University sponsored studies.
- The notification process to REC, HRA, MHRA and other regulatory bodies.

3. Who

This SOP is aimed at Chief Investigators (CI), students, trial coordinators and other members of University Staff involved in processing modifications and obtaining University, ethical, and regulatory approvals.

The SOP is also aimed at staff within the University Clinical Research Governance Team who are involved in the review process of study modifications for University Sponsored studies.

4. When

This SOP should be referred to when making any modification to a University Sponsored study.

5. Definitions of modifications

A modification to a research study can be a **substantial modification, a modification of an important detail** or a **minor modification.**

Determining the substantiality of a modification, and whether a proposed change is significant or insignificant will continue to be the responsibility of the sponsor. ALL modifications must be submitted to the Sponsor in the first instance as per Section 6 of this SOP.

Substantial modifications

A substantial modification is a modification to a clinical trial approval which is likely to have a substantial impact on the safety or rights of participants or on the reliability or robustness of the data generated by the trial.

The changes below are examples of substantial modifications[1]:

- temporary halt of the trial or temporary halt at a trial location within the UK and restart of the trial
- significant changes to participant facing documentation, recruitment and consent procedures or inclusion and exclusion criteria
- change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study
- change of the chief investigator
- change of the main objective, primary or secondary endpoints, trial design (including addition of a new arm or placebo group)
- protocol modification due to new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk and benefit assessment
- any other change of study design likely to have a significant impact on primary or major secondary statistical analysis or on the risk and benefit assessment

Substantial modifications to CTIMPs are further classified as Route A or Route B, and the MHRA will process a substantial modification differently depending on whether it is Route A or B;

- Route A substantial modifications are 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 specific, low-risk, or previously approved modifications, such as incorporating new safety data without altering the protocol or updating reference safety information. The Route B pathway allows for streamlined, automatic approval of such modifications

Modification of an important detail

This is a modification that does not significantly impact participant safety or rights, which the MHRA and REC only need to be made aware of for administrative or oversight purposes. These types of modification are not reviewed by the REC or MHRA and no outcome will be issued. They are for

[1] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/clinical-trial-regulations-reform/guidance-on-changes-to-the-clinical-trials-regulations/definitions-and-terminology/update-to-amendment-terminology/#SubstantialModifications

information only. These modifications may however need other approvals (for example HRA and HCRW approval).

The changes below are examples of modifications of an important detail[2]:

- changes to the trial identification (for example the trial title)
- submitting the date that the first UK trial participant is recruited
- increase in duration of the trial, provided that the exposure to treatment is not extended, the definition of the end of trial is unchanged and there is no change to monitoring arrangements
- change to contact details for named contacts for the trial, for example the sponsor, sponsor representative or chief investigator
- change of investigator (other than the chief investigator) at a trial location in a multi-centre trial
- addition of new trial locations not listed with the original request for authorisation and REC application where there are no additional documents for submission
- change of the sponsor's legal representative
- change of the sponsor[3]

Minor modifications

Minor modifications are changes that do not fall into the category of 'substantial modification' or 'modification of an important detail'.

The changes below are examples of minor modifications[4]:

- changes in the number of participants per trial location, if any change is insignificant in view of the absolute number of participants
- changes in the processes associated with recording keeping used by the research team for recording trial data

[2] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/clinical-trial-regulations-reform/guidance-on-changes-to-the-clinical-trials-regulations/definitions-and-terminology/update-to-amendment-terminology/#ModificationImportantDetail

[3] A change of sponsor will become a modification of an important detail under the 2025 regulations. This is because it will no longer be a legal requirement for the REC to consider the suitability of the sponsor. If the change in sponsor would require changes to insurance arrangements and/or study documents (beyond only changing the name of the sponsor within study documents) then this would be a substantial modification.

[4] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/clinical-trial-regulations-reform/guidance-on-changes-to-the-clinical-trials-regulations/definitions-and-terminology/update-to-amendment-terminology/#MinorModification

- internal changes to the sponsor's organisation
- changes in the logistical arrangements for storing or transporting samples
- changes in technical equipment
- minor changes to the protocol or other study documentation, for example correcting errors, updating contact points, minor clarifications

6. Submission of Modifications for Sponsor Review

Prior to submission to external review bodies, the CI is required to notify the Sponsor [the Clinical Research Governance Team (CRGT)] of the proposed modification, in order that the modification be reviewed and assessed for suitability and substantiality and a decision made on the appropriate external review bodies to which it must be submitted.

For studies that were reviewed and approved by NHS REC the HRA Modification Tool must be used to notify the Sponsor of the modification. This can be download via IRAS - https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

Research Tissue Banks (RTBs) and Research Databases (RDBs) should continue to use the Notice of Substantial Amendment Form generated in IRAS to notify substantial amendments to the Sponsor and REC.

If a modification is required to a study that was not approved by NHS Ethics (i.e. University Ethics) then FORM003[5] should be completed and submitted for Sponsor review.

The form submitted should contain detailed information regarding the modification to assist the Sponsors review of substantiality.

All modified documents must also be provided for review, with changes highlighted using the 'Track Changes' function in Microsoft Word.

Where a study is Co-Sponsored with an NHS Trust the University will require confirmation of NHS Co-Sponsor review and approval of the modification prior to submission to external review bodies.

The Liverpool Health Partners (LHP) Joint Research Office (JRO) Sponsorship Committee and Non-Interventional Sponsorship Sub Committee (NISSC) retain overall responsibility for reviewing and approving modifications, however the function of review is undertaken by the Chair of the respective Committee that approved the initial Sponsorship Application. This will be assessed depending on which Committee undertook the initial review of the application. If the Chair feels that the modification requires further review the Committee will review the full modification at the next committee meeting.

[5] Modification Approval Form

Minor modifications or Modification of an important detail which do not affect the scientific integrity of the study (i.e. addition of new locations, extension to study period) may be pre-approved by the Responsible Sponsor Officer and presented for information to the Chair.

A summary report of modifications reviewed will be made available at the next committee meeting for ratification.

Upon receipt of the completed HRA Modification Tool, IRAS Modification Form (for RTBs and RDBs) or Sponsor Modification Approval Form, all amended documentation, and co-sponsor confirmation (where applicable) the Chair of the appropriate Sponsorship Committee will review and assess the modification. As above, if the modification may be subject to full committee review if it is large or complex. The CTU/CI will be informed of the decision within 5 working days.

7. Submission of Modifications to NHS REC and HRA

Note - This section only relates to projects submitted through the standard part of IRAS only. All trials submitted through the Combined Review service via the new part of IRAS, should consult Section 10.

Following review and approval of the modification the Clinical Research Governance Team will contact the applicant with details of the required submissions as detailed in the HRA Modification Tool.

All modifications must be submitted via the Online Submission system - http://www.myresearchproject.org.uk/amendment.

The online modification submission functionality requires you to log in to the IRAS Identity Gateway, which is separate login to your main IRAS account. If you have not used it before you may need to set up a new account. Please follow the on-screen instructions and refer to the guidance under 'Help' on the login page.

When you have logged in, refer to the on-screen step-by-step instructions which will guide you through the process. You will be asked to enter the IRAS ID and answer some simple questions about your modification. Some of these questions require you to enter information exactly as it appears on the Modification Tool, so have this available to refer to.

You can then upload all documentation relating to your modification and proceed to submit. You can drag and drop up to 15 documents at a time into the upload drop box. Please note that file names for supporting documents must contain fewer than 60 characters (including spaces).

Upon submission you will receive an automated email to confirm submission of your modification. The modification will be shared with REC and/or for study-wide review as applicable.

8. Submission of Modifications for Research Tissue Banks and Research Databases

The completed Notice of Substantial Amendment form should be electronically authorised by all parties listed on the form's authorisations tab in IRAS.

When authorisations are in place, submit of the final PDF of the form (created via the Submission Tab of amendment form) to the REC, together with all relevant enclosures via online amendment submission according to the instructions provided on the amendment form's submission tab.

Non-substantial amendments for RTB and RDB projects do not need to be notified to the REC.

If you wish to update the REC of any minor changes, for example to update key study personnel contact details, you can do this by email.

9. Submission of CTIMP Modifications to MHRA

Note - This section only relates to projects submitted through the standard part of IRAS only. All trials submitted through the Combined Review service via the new part of IRAS, should consult Section 10.

As above, all modifications must be submitted via the Online Submission system - http://www.myresearchproject.org.uk/amendment.

When notifying the MHRA of a substantial modification to a CTIMP, the following must be included in the submission:

- Covering letter including the following;
    - all relevant trial identifiers, including the full trial title (and abbreviated title where appropriate), protocol number, IRAS ID (for trials approved through combined review) or EudraCT number (for trials not approved through combined review), and any global identifiers such as an EU CT number
    - a statement explaining why the applicant considers the modification to be a Route A or Route B substantial modification
    - an outline of the substantial modification, with clear justification for changes
    - an outline of any minor changes to the clinical trial approval to be made alongside the proposed substantial changes
    - an outline of minor changes that have already been implemented, even if unrelated to the proposed substantial modification
    - for resubmissions, highlight the changes made compared to the previous submission
    - a table of all submitted documents, including version numbers and dates
    - a purchase order number for invoicing for fees applicable to submission of an application to modify a clinical trial approval[6]

[6] https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#clinical-trials-application-fees

- A PDF copy of the locked Modification tool. You should ensure that the modification tool contains a clear description of the modification and reasons for the proposed changes.

  Depending on the nature of the modification the following may also be required;

  - if the modification affects the information on the original medicines form, an updated copy should be submitted (the form can be requested from clintrialhelpline@mhra.gov.uk for non-combined review trials)
  - if the modification affects the documents submitted alongside the original clinical trial approval application (e.g. the protocol, IB, or IMP dossier), the application must list the changes to the approved document, which should include:
    - a comparison of the previous and new wording and justification for each substantial change
    - updated data summaries and risk and benefit assessments, if applicable, with consideration given to the consequences of the modification for trial participants and for the evaluation of results
    - highlighting any minor changes made to these documents
  - if the modification affects the documents submitted alongside the application for clinical trial approval (for example, the protocol, IB, or IMP dossier), a copy of the document with the changes shown in markup should be submitted
  - if the modification affects the documents submitted alongside the application for clinical trial approval (for example, the protocol, IB, or IMP dossier), a clean copy of the new document should be submitted

10. Submission of CTIMP Modifications through the Combined Review service

For trials that have been submitted via the Combined Review service it still required that the HRA Modification Tool is completed and submitted to Sponsor as outlined above.

Once Sponsor approval has been obtained the modification needs to be created via the Combined Review service part of IRAS (http://www.myresearchproject.org.uk/CWOW).

From 'My Projects' you will be able to create modifications for any projects with an 'approved' status.

All details entered must match the information on the approved Modification Tool. If incorrect information is entered it may result in your modification being rejected and you will need to create and submit a new one.

You will then need to upload supporting documentation as detailed in Section 9

Unlike submitting an initial application, there is no process for the regulator to request further information (RFI) for modifications. However, you may be contacted by email or telephone to provide some information or clarification if this is required before issuing a final opinion.

11. Submission of Modifications to MHRA Devices

The following applies to modifications to clinical investigations of medical devices subject to regulation by the Competent Authority.

You must notify MHRA Devices of all proposed changes to the investigation (not only those classified as substantial modifications for the purposes of ethical review) and await a letter of no objection from MHRA Devices before you implement them. This includes changes made at the request of the REC. Failure to notify proposed changes could result in the manufacturer being liable to prosecution.

When notifying MHRA of changes, please provide the following information in writing:

- the MHRA reference number for the trial;
- details of the proposed change(s) to the clinical investigation plan or the design of the device;
- the reason for the change(s); and
- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.
- A copy of the completed Modification Tool

Notifications should be sent directly to MHRA Devices via CI-amendments@mhra.gov.uk.

12. Submission of Modifications to other Regulatory bodies

If a study has obtained approvals outside of the IRAS system (i.e. University of Liverpool Ethics or International Ethics) then the CI should ensure familiarity with the submission processes for each body. The Clinical Research Governance Team will advise where required.

IRAS outlines the guidance for submission of modifications to other Regulatory Bodies - https://www.myresearchproject.org.uk/help/hlpconfidentiality580.aspx

13. Urgent Safety Measures to CTIMPs – Notification to Sponsor

The Sponsors and CI may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. Where the University is Sponsor of a CTIMP they need to be informed at the earliest opportunity following the identification of the need for an Urgent Safety Measure (USM).

The Clinical Research Governance Team should be notified of any Urgent Safety Measure immediately, to enable proper oversight and review of the required measure. This can be done in parallel with discussions with the MHRA, detailed in Section 14.

The Urgent Safety Measure will be reviewed and approved by Chair's action and submitted for ratification at the next LHP JRO Sponsorship Committee.

Notification of Substantial Modification is also required for USMs and should be submitted to Sponsor in line with section 6.

14. Urgent Safety Measures to CTIMPs – Notification to MHRA

Call the MHRA's Clinical Trials Unit on 020 3080 6456 to discuss the issue with a medical assessor, ideally within 24 hours of measures being taken. Please call no later than 3 days from the date the measures are taken.

After discussing the USM with the MHRA assessor via phone you must provide the MHRA with written notification of the measures taken and discussed with the medical assessor, within 7 days from the date the measures were taken, or as soon as possible. For trials not approved via Combined Review you will be instructed to send an email to the medical assessor who assessed the USM over the phone, clintrialhelpline@mhra.gov.uk.

If you are not able to report a USM to the MHRA via the phone please send an email to clintrialhelpline@mhra.gov.uk within 3 days of taking urgent measures. The subject of the email will be 'USM for trial IRAS ID/EudraCT number'. Please explain in the email the USM implemented, the reason and why you did not report it via phone. An MHRA assessor will contact you and provide advice regarding further actions.

If the trial has gone through the Combined Review process, then the USM written notification should be submitted via the Combined Review section of IRAS (http://www.myresearchproject.org.uk/CWOW).

Notification of a substantial modification is also required. The substantial modification covering the changes made as part of the USM should be submitted within approximately two weeks of notification to the MHRA. Submission should be made in line with sections 9 and 10 (as applicable).

15. Roles and Responsibilities

It is the responsibility of the CI to identify and make modifications to the study as required. Where this function is delegated to a CTU or member of research team it must be appropriately documented. In any case the CI must sign off each modification notification form.

The CI must inform the Sponsor of any proposed modifications who are responsible for assessment of substantiality.

The CI must then submit the modification to regulatory authorities as directed by the Sponsor. Approvals must be obtained before approaching NHS Trusts to gain ongoing Confirmation Of Capacity And Capability or R&D approval. An exception to this is urgent safety measures which may be made immediately.

It is the responsibility of the CI to ensure that the local Investigator has submitted modifications to the local R&D Department and gain their approval for them prior to implementation of those modifications. At all times the Sponsor will have oversight of the process.

16. Abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
IRAS	Integrated Research Application System
JRO	Joint Research Office
HRA	Health Research Authority
MHRA	Medicines for Healthcare Products Regulatory Agency
REC	Research Ethics Committee
University	University of Liverpool

17. Associated Documents and References

FORM003 Modification Approval Form

UK Policy Framework for Health and Social Care Research

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025

MHRA Amending your trial protocol or other documentation guidance

HRA Amending an approval guidance

18. Training and Resources

CIs, students, trial coordinators and other members of University Staff involved in preparation and submission of modifications should be aware of and familiar with this SOP. Training can be provided by the Clinical Research Governance Team upon request.

19. Monitoring and Audit

An internal audit of Clinical Directorate SOPs will be conducted at a minimum of every two years.