SOP number	**51.021**	Version	**6.0**
Title	**Review and Approval of Modifications for Research Sponsored by NHSGGC or Co-Sponsored by NHSGGC and the University of Glasgow**		

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SOP category	NHS GG&C Sponsor R&I

Staff category

Staff Category	**R**	**A**	**C**	**I**
Research Governance Manager		X		
R&I Systems & Operations Manager			X	
Chief Investigators	X			
Sponsor Research Co-ordinators	X			
Innovation Sponsor Co-ordinator	X			
Innovation Project Managers	X			
Sponsor Research Facilitator	X			
Senior Research Administrators	X			
Innovation Contracts Manager	X			
R&I Sponsor Pharmacy	X			
Project Management	X			
Research Governance	X			
University of Glasgow Research Regulation and Compliance Team			X	
Principal Investigator				X

1. Scope

This procedure applies to NHS Greater Glasgow and Clyde (NHSGGC) Research staff involved in the assessment, review and approval of modifications to studies sponsored by NHSGGC or Co-Sponsored with the University of Glasgow (UoG).

2. Purpose

To describe the process for Sponsor review and approval of modifications (formerly amendments) to appropriate organisations, departments and individuals for studies when NHSGGC are the Sponsor or Co-Sponsor with UoG. This procedure applies to research studies, CTIMPs (Clinical Trials of Investigational Medicinal Products) and CIMDs (Clinical Investigations of Medical Devices).

3. Procedures

3.1. Background

From 28 April 2026, changes to approved studies will no longer be called 'amendments'; they will be referred to as 'modifications'. Modifications are categorised as substantial modifications (SM), modifications of an important detail (MOID) and minor modifications (MM). Changes to documents before initial regulatory submissions are not modifications and continue to be handled as per SOP 51.014.

The Sponsor Research Co-ordinator (SRC), Innovation Sponsor Co-ordinator (ISC) and the Sponsor Research Facilitator (SRF) are responsible for determining the appropriate modification classification and for authorising submission of modifications to the Research Ethics Committee (REC) and/or Medicines and Healthcare products Regulatory Agency (MHRA). The SRC and Innovation Project Manager (IPM), or delegate such as Glasgow Oncology Clinical Trials Unit (GO CTU) Project Manager (PM), are responsible for submitting modifications to the MHRA for any legacy studies which were not submitted via Combined Review. For combined review studies, the responsibility lies with the Chief Investigator (CI) or an appropriate delegate, such as the PM. Designated staff working across GO CTU will process and approve modifications as per this SOP and relevant GO CTU SOPs.

Local Management Approval is required for study locations, depending on the category of modifications (see Section 3.1.2.). For NHSGGC sites, this process is detailed in SOP 52.003, with the addition of Section 3.7 for NHSGGC Sponsored or Co-Sponsored studies.

3.1.1. Modification Classification

Modifications are classified in accordance with the UK Clinical Trials Regulations and associated HRA/MHRA guidance as follows:

1. **Substantial Modification**
   A modification that 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 study.

2. **Modification of an Important Detail (MOID)**
   A modification that does not significantly impact the safety or rights of participants but of which the relevant regulatory or ethics bodies, as applicable, must be aware for administrative or oversight purposes. Modifications of an important detail are not subject to MHRA or REC review and no regulatory outcome is issued.

3. **Minor modification**
   A modification that does not meet the criteria for a substantial modification or a modification of an important detail. Minor modifications may be implemented without notification to the MHRA or REC at the point of implementation, although appropriate records must be retained and other approvals (e.g. governance or contractual) may still be required.

Examples of substantial modifications, modifications of an important detail and minor modifications are detailed in Appendix 1.

3.1.2. Route A and Route B Substantial Modifications (CTIMPs)

For CTIMPs, substantial modifications are further classified as Route A or Route B for MHRA processing.

- **Route A substantial modifications**
  Substantial modifications that are likely to have a significant impact on the safety or rights of participants or on the reliability or robustness of the trial data and require full regulatory review by the MHRA (and REC, where applicable) prior to implementation.

- **Route B substantial modifications**
  These are substantial modifications which are pre-defined lower risk changes that meet MHRA-specified criteria (see Appendix 2) and for which the Sponsor confirms that no new significant safety concerns have arisen. Route B modifications are eligible for a streamlined MHRA process, while still requiring appropriate ethical review where applicable.

3.1.3. Modification Categorisation (As Category A, B or C)

In addition to regulatory classification, modifications are categorised for NHS Research & Innovation (R&I) continuing management approval using Category A, B or C, as indicated by the Integrated Research Application System (IRAS) Modification Tool.

- **Category A**
  A modification that impacts or affects all participating NHS organisations. All participating NHS organisations are required to review the modification to determine whether they are able to continue to support the study.

- **Category B**
  A modification that impacts or affects specific participating NHS organisations only. Review is required only by those NHS organisations affected by the modification to determine whether continued support for the study can be provided.

- **Category C**
  A modification that has no impact on NHS organisations and therefore does not require local R&I management approval or governance review. Category C modifications should still be shared for information as appropriate.

For Category A and B modifications, participating NHS organisations have up to 35 calendar days from notification to raise an objection. Where no objection is raised within this period, the modification may be implemented, subject to any required regulatory approvals being in place. Local R&I management approval is not required for the following Category B modifications:

- Changes solely involving the appointment or replacement of a Principal Investigator (PI) at other study locations
- Addition solely of a new study location (except at that study location)

Category C modifications may be implemented immediately, provided any applicable regulatory requirements are met. Oversight of modification implementation and co-ordination across study locations is the responsibility of the CI or an appropriately delegated individual, such as the PM.

3.2. Preparation of Modification and Submission to Sponsor

The CI or delegate will complete the Modification Tool from the IRAS website. The tool will recommend the modification classification (Section 3.1.1) and categorisation (Section 3.1.2) based on the responses provided.

Depending on the type of study, the completed Modification Tool, together with all revised documentation and relevant correspondence, will be submitted to the appropriate Sponsor representative, Senior Research Administrator (SRA), SRC, ISC or SRF as well as any other relevant Sponsor stakeholders, for sponsor review. The Modification Tool will be drafted and shared with the Sponsor at the earliest appropriate opportunity, to provide a clear overview of all proposed changed.

On receipt of a modification, the SRA will:

- Notify the appropriate SRC, ISC or SRF and create a new study modification sub-folder in both the email repository and the study e-File, labelled with the modification reference, date and category (e.g. *01. SM01 12.05.2026 Cat A*). Modifications will be named by type i.e. substantial modification: SM, modification of an important detail: MOID and minor modification: MM followed by a 2-digit number (e.g. 01, 02, etc.), numbered sequentially in order of receipt by R&I, irrespective of modification type.
- Save all modification-related documents in the modification sub-folder and move all associated correspondence into the corresponding email sub-folder.
- Ensure a blank copy of Form 51.021B (Modification Log) is saved in the modification folder for the study (if not already present).
- Save a blank copy of Form 51.021C (Sponsor Review of Modification Checklist) in the relevant modification sub-folder.
- Registers the modification on the 'Post Approval' tab on SReDA with full details and a status of 'Pending' (for Category C modifications, the status should be recorded as Category C).
- For single centre studies, create a new modification folder within the 'Documents' tab in SReDA.

3.3. Review of Modification Prior to Submission to REC and/or MHRA

The SRC, ISC or SRF will review the completed Modification Tool, ensuring it reflects the modified documents and the modification categorisation is appropriate. It is the Sponsor's responsibility to determine (risk-based) whether a change is substantial, an important detail, or minor; and for CTIMPs, whether a substantial modification is Route A or Route B, which will be done by the SRC using the MHRA's decision tree:
https://assets.publishing.service.gov.uk/media/69e63b638c9f882ae5997f86/Fig1._Modification_types.pdf

Before signing and locking the Modification Tool, the SRC, ISC or SRF will complete Form 51.021C (Sponsor Review of Modification Checklist) and will:

- Review all modified documents (as per SOP 51.001 and 51.002) and provide feedback, taking into account input from relevant stakeholders.
- For CTIMPs, liaise as appropriate with pharmacy, pharmacovigilance, project management, monitoring, study statistician and data management teams. Relevant decision-making correspondence will be retained within the TMF (as per SOP 51.016).
- For substantial modifications relating to CTIMPs, ensure the Sponsor Review Checklist is reviewed by another suitably qualified Sponsor representative appropriate to the change being proposed (e.g. Sponsor Pharmacist, Pharmacovigilance Manager, Monitor, Sponsor Research Co-ordinator etc.) before Sponsor authorisation is provided.

- Confirm any costs implications with R&I Finance and the funder, and re-cost any project changes as required in accordance with SOP 51.010.
- For co-sponsored studies, liaise with the UoG Research Regulation and Compliance team and confirm implications on insurance and contractual arrangements, and ensure these are updated as required.
- Confirm implications for support from all relevant NHS departments, including feasibility and any required Head of Department (HoD) approvals.
- Review and update contractual arrangements where applicable (as per SOP 51.039), and detail on Form 51.021C).
- Assess if the modification could potentially have a negative impact on agreed study milestones or timelines.
- Assess whether the modification requires re consent of participants already recruited to the study.
- Assess any change in study's risk profile in consultation with the wider Sponsor team and Trial Management Group (TMG), where one is in place in line with Section 3.3.2.

Once Sponsor review is complete and the Modification tool is locked the SRC, ISC or SRF (or appropriate delegate such as an SRA) will:

- Issue the standard Sponsor modification decision email (Form 51.021A) to the CI (and PM where appropriate) confirming the Sponsor's decision, enclosing the locked Modification Tool and a list of reviewed documents, confirming that submission to the REC and/or MHRA may proceed.
- Retain evidence of Sponsor communication within the study e-Folder and in the TMF for CTIMPs/CIMDs.
- Update the Modification Log (Form 51.021B).

3.3.1. Uncertainty with Classification or Categorisation

In most cases, modification classification and categorisation is straightforward to determine. However, if a modification is submitted where there is uncertainty or disagreement, this must be escalated through relevant governance structures, R&I Senior Management and, where appropriate, discussed directly with the regulatory authority. Once a decision is made, the justification must be included in Form 51.021C.

3.3.2. Assessment of Risk

The SRC, ISC or SRF will assess the impact of the modification on the risk to research participants and the Sponsor including potential effects on participant safety and data integrity. Any pharmacy-related changes will be assessed by an appropriate person in the Sponsor Pharmacy team and any financial/resource implications will be discussed with the R&I Finance and grant holder(s).

For CTIMPs/CIMD, the existing risk assessment completed in accordance with SOP 51.004 will be reviewed to determine whether the modification results in a material change to the risk profile of the study. Where the modification increases risk or has the potential to affect participant safety or the validity of study outcomes, the SRC or ISC will update the risk assessment accordingly using Form 51.004D as per SOP 51.004. In the event the modification is determined to have no impact on the existing risk assessment, this decision and supporting rationale will be documented in Form 51.021B and Form 51.021C.

3.4. Submission of Modification to REC and/or MHRA

Once Sponsor review of the proposed modification is complete, the CI (or delegate) will submit the locked Modification Tool along with all Sponsor approved revised documentation via IRAS.

For CTIMPs not originally approved through the Combined Review process or CIMDs, additional submission to the MHRA will be undertaken by the SRC, IPM or GO CTU PM via the MHRA Submissions portal.

For CTIMPs approved through the Combined Review process, modifications will be submitted by the CI or delegated PM and authorised by the SRC as a single Combined Review submission via IRAS, which routes the application to the REC, HRA and MHRA as required. Substantial modifications must also be classified by the SRC as Route A or Route B (see Appendix 2) and must be outlined in the cover letter to the MHRA The SRC will complete the CTIMP Template Substantial Modification Cover Letter (Form 51.021E) and request the trial pharmacist to review and provide justifications to the specified changes, CI will also be asked to review where appropriate.

3.4.1. Minor Modification Notifications to REC and/or MHRA

Under the Clinical Trials Regulations, minor modifications do not require notification to the REC or MHRA. However, NHSGGC Sponsor requires all modifications, including minor modifications, to be submitted via the IRAS Modification Tool in order to ensure appropriate Sponsor oversight, transparency and audit readiness. Submission via IRAS will be used to record the modification and determine any associated governance actions and will not delay implementation unless additional approvals are required. Communication and filing will be undertaken as described in Section 3.9.

3.5. Modification REC and/or MHRA Approvals

Where REC and/or MHRA approval is required based on the modification classification, the relevant approvals must be in place before implementation (as per SOP 52.003). Evidence of the applicable approvals will be recorded in Form 51.021B and Form 51.021C.

3.6. Notification of Modification to Trial Locations

When a modification has been given REC favourable opinion and/or MHRA approval (dependent on the classification of research), the CI (or delegate such as PM) will circulate the modification details, supporting documentation and approvals to study locations and inform them when this can be implemented (e.g. when all local approvals have been received and, where applicable, any updates to the eCRF, contracts or localised documents have been completed) as per SOP 56.003. For studies conducted in Scotland, submission of a modification via IRAS will automatically route the modification to NHS Research Scotland Permissions Coordinating Centre (NRS PCC), who will then notify the relevant Scottish NHS R&D offices.

3.7. Process for NHSGGC Local Management Approval of Modifications

For NHSGGC-sponsored/co-sponsored studies, where required, Local Management Approval will be issued by the SRA, as detailed in SOP 52.003. In addition, for NHSGGC-sponsored studies, the SRA must: ensure all requirements stated in Section B of Form 51.021C are met before issuing Local Management Approval confirmation, update Section B of Form 51.021C and SReDA accordingly. The SRA will also notify any support departments listed in Section B of Form 51.021C.

3.8. Urgent Safety Measures

Following the implementation of an Urgent Safety Measure (USM) as detailed in SOP 53.001, any consequential changes to study documentation must be submitted as a substantial modification to the relevant review bodies in a timely fashion. The submission must follow standard substantial modification procedures and clearly reference the USM, including a justification for its immediate implementation.

3.9. Modification Filing Requirements

For CTIMPs and CIMDs, all documentation relating to the review and approval of modifications must be filed within the appropriate section of the TMF as per SOP 51.016 and Form 51.016A. Working copies of all documentation will also be retained in the study e-File. For all other studies, all documentation relating to the review and approval of modifications must be filed within the appropriate section of the e-File as per SOP 51.042.

4. Referenced Documents/Links

- Form 51.021A: Modification Type Confirmation
- Form 51.021B: Modification log
- Form 51.021C: Sponsor Review of Modification Checklist
- Form 51.021E CTIMP Template Substantial Modification Cover Letter
- SOP 51.001: Protocol Development
- SOP 51.002: Participant Information Sheet and Informed Consent Form Development for Research Sponsored by NHSGGC or Co-Sponsored by NHSGGC and the University of Glasgow
  SOP 51.004: Risk Assessment
- SOP 51.014: Preparation and Initial Submission of Research Studies to the Research Ethics and Regulatory authorities IRAS/Combined Review Forms for Sponsored & Co-sponsored Studies
- SOP 51.016: Preparation and Maintenance of a Trial Master File
- SOP 51.039: Contracts Management for Research Sponsored by NHSGGC or Co-Sponsored by NHSGGC and the University of Glasgow
- SOP 51.041: Preparation and Maintenance of a Non-CTIMP Sponsor e-File
- SOP 52.003: R&I Review of Amendments
- SOP 53.001: Handling Urgent Safety Measures for Clinical Trials for Investigational Medicinal Products
- SOP 56.003: Project Management: Managing an Active Trial
- Form 51.004E: Update to Risk Assessment Form
- Form 51.016A: Sponsor TMF Index
- https://www.gov.uk/guidance/guidance-on-substantial-modifications-to-a-clinical-trial
- Update to 'amendment' terminology - Health Research Authority
- https://assets.publishing.service.gov.uk/media/69e63b638c9f882ae5997f86/Fig1._Modification_types.pdf
- Route B substantial modification pilot - GOV.UK

5. Related Documents

- NRES guidance: http://www.nres.nhs.uk
- MHRA guidance: http://www.mhra.gov.uk
- IRAS Help - Maintaining your approvals - Modifications (myresearchproject.org.uk)
- https://assets.publishing.service.gov.uk/media/68dbc85949e17d00a56ffc12/Fig3._Route_B_substantial_modification_applications.pdf

6. Document History

Version	Date	Description	Retrospective Implementation
1.0	06/09/13	Release of First Version	No
2.0	08/01/16	Minor changes to section 5.2.1	No
3.0	14/07/2016	Renumbered with minor changes on process for informing stake holders	No
4.0	02/03/2020	Temp. author change. Staff category updated to include relevant staff groups. "Research Co-ordinator replaced with "Sponsor Research Co-ordinator" to clarify responsibility of this staff group. 5.3.1 updated to reflect revised process in response to audit finding. Version updated.	No
5.0	04/10/2024	Version no and author change with additional information to clarify the amendment review process. The title was updated to include co-sponsorship scenario. Included Appendix 1 with Examples of substantial and non-substantial amendments, as per HRA guidelines. Three new forms were introduced: - Form 51.021B - Amendment Log – to capture an overview of all modifications of a study/trial - Form 51.021C - Sponsor Review of Amendment Checklist – to capture sponsor review, processing and local approval of amendments - Form 51.021D - Management Approval is still valid - email template Additional information on sponsor process for review and local approval of amendment with clarity on SRA/RA and RC/ICM/RF associated tasks. Cancer Research UK-CTU updated to Glasgow Oncology-CTU	No
6.0	26/05/2026	Updated to align with the new MHRA regulations; the local management approval process has been reduced as is process now governed under SOP 52.003, and Form 51.021D has been withdrawn as it is covered in Form 53.003B. Form 51.021E: CTIMP Template Substantial Modification Cover Letter added.	Yes – 28/04/2026

Appendix 1: Examples of Modifications

Examples of substantial modifications, modifications of important detail and minor modifications, as per HRA guidelines:

1. **Substantial Modifications**
   - temporary halt of the trial or temporary halt at a trial location within the UK
   - re-start of the trial following a temporary halt
   - significant changes to participant information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, and other similar documents (whether generic to the whole study or specific to a particular trial location)
   - significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial
   - significant increase or decrease to the radiation exposures to participants from the protocol
   - change of insurance or indemnity arrangements for the trial
   - change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator or collaborator
   - change of the chief investigator
   - any other significant change to the conduct or management of the trial at particular trial locations
   - any other significant change to the terms of the original REC application
   - change of the main objective of the trial
   - change of primary or secondary endpoints likely to have a significant impact on the safety or scientific value of the trial
   - 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
   - addition of a trial arm or placebo group
   - significant change of inclusion or exclusion criteria (for example age range) likely to have a significant impact on the safety or scientific value of the trial
   - change of a diagnostic or medical monitoring procedure likely to have a significant impact on the safety or scientific value of the trial
   - withdrawal of an independent data monitoring committee
   - 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

2. **Modification of an Important Detail**
   - 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

- changes in the number of participants per trial site, 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
- 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

Appendix 2: Route B Substantial Modification (CTIMPs only) – Eligibility Criteria as per MHRA guidelines

A substantial modification may be classified as Route B only if all core criteria are met and at least one of the permitted conditions applies.

1. **Core criteria (must all be met)**

The Sponsor has made reasonable enquiries and is satisfied that:

- No new significant safety concerns arise from the modification; and
- No new significant safety concerns are introduced in relation to any Investigational Medicinal Product (IMP) involved in the trial.

2. **Permitted Route B conditions (at least one must apply)**

The modification must meet one or more of the following conditions:

Condition A — Prior approval

- The trial is not first-in-human, and
- The same modification has already been approved by a recognised regulatory authority in the EU, EEA, or USA.

Condition B — Limited protocol changes

- The modification is limited to a defined set of protocol changes, such as:
    - Changes to study design
    - Objectives
    - Assessments or measurements

Condition C — Limited IB / SmPC changes

- The modification is limited to pre-defined changes to:
    - The Investigator's Brochure (IB), or
    - The Summary of Product Characteristics (SmPC)
      Examples include safety updates or revised adverse event frequencies, where the overall risk profile is unchanged.