

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	1 of 19	Approval Date: 15/04/2026
Reference Number: UHB 536		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2026
Approved By: Joint Research Governance Group		

<b>Reference Number:</b> SOP/003/06 <b>Version Number:</b> 2.0	<b>Date of Next Review:</b> 15/04/2029
<b>MANAGING MODIFICATIONS FOR CARDIFF JRO SPONSORED RESEARCH</b> <b>Standard Operating Procedure</b>	
<b>Introduction and Aims</b>	
<p>In April 2026 the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 came into force. These impose legal standards on the conduct of all interventional clinical trials involving medicines. Researchers must ensure that procedures are in place to comply with the regulations and relevant guidelines and directives e.g. Good Clinical Practice (GCP) for clinical trials.</p> <p>Under the <i>Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (hereinafter referred to as the UK Clinical Trials Regulations)</i>, any changes made to approved studies will no longer be called 'amendments'.</p> <p>Instead, they will be referred to as 'modifications'.</p> <p>The Health Research Authority (HRA) will also adopt this updated terminology to ensure consistency across UK clinical trial governance. These updates are designed to harmonise ethical and regulatory processes under the new Medicines and Healthcare Products Regulatory Agency (MHRA) framework and align with international standards.</p> <p>Modifications are any changes made to a research project after the favourable ethical opinion and/or the MHRA, Health Research Authority (HRA)/Health and Care Research Wales (HCRW) approval has been issued. Modifications are categorised as either substantial modifications, modifications of an important detail or minor modifications. Substantial modifications to a Clinical Trial of an Investigational Medicinal Product (CTIMP) can be further categorised as Route A or Route B.</p> <p>To make a change to a research project within the United Kingdom, researchers must create and submit a modification for review by their allocated Research Ethics Committee (REC), the MHRA and/or the HRA/HCRW. Once a modification has received the relevant approvals, including confirmation of continued Capacity and Capability/no objection from the R&amp;D Office at each participating NHS organisation, the changes outlined as part of that modification may then be implemented.</p> <p>This Standard Operating Procedure (SOP) sets out the process by which modifications to clinical research projects should be submitted for REC, the MHRA, and/or HRA and HCRW review and approval. This guidance is designed to assist researchers prepare modifications using the IRAS Modification Tool and submit to the correct review bodies via the IRAS submission portal.</p>	
<b>Objectives</b>	
<p>To describe the process of preparing a modification for submission, including their classification as substantial (Route A or Route B), modifications of an important detail, or minor, and obtaining Sponsor authorisation prior to submission to reviewing bodies.</p>	

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	2 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

Provide guidance on submission to the reviewing bodies, the external review process and authorisations required before implementation of modifications.

Guidance on notifying NHS Research and Development (R&D) Offices and Investigators.

Provide timelines and guidance on the implementation of modifications and Urgent Safety Measures: their implementation and notifications required.

### Scope

This SOP should be used by CIs and other members of the research team involved in preparing and submitting modifications for studies sponsored by a Joint Research Office (JRO) organisation; Cardiff and Vale UHB (CAVUHB) or Cardiff University (CU).

For CTIMPS or Clinical Trials of a Medical Device, this may include external Clinical Trials Unit (CTU) staff.

### Responsible Personnel:

It is the responsibility of the CI, or an appropriately delegated member of the research team or CTU, to notify the Sponsor of any modifications to a research project and draft the associated modification documentation. Any such delegation should be formally recorded in writing in the study delegation log. The decision to implement a modification for a study is normally a collaborative decision, agreed with the members of the Trial Management Group (TMG) for larger studies. In the case of smaller studies, the decision to modify an aspect of a study will normally involve a discussion between the CI, Study Manager or Research Assistant and/or NHS Investigator(s) and the Sponsor.

It is the responsibility of the Sponsor representative to review all project documentation altered as part of a modification submission and assess the modification to confirm the correct categorisation (e.g., substantial modification, modification of an important detail, or minor modification). This is usually done in collaboration with the study team or CTU. The Cardiff JRO Research Governance Team are responsible for assessing modifications for CAVUHB and CU Sponsored studies.

Once a modification has been authorised by the Sponsor representative, it is the responsibility of the CI, or an appropriately delegated member of the research team or CTU, to submit the modification via the [IRAS Identity Gateway](#) website or the [Combined Review Service](#) (as appropriate), and notify any participating organisations (NHS or non-NHS) of the submission.

### Equality Impact Assessment

An Equality Impact Assessment has not been completed. This is because this procedure has been written to support the implementation of the Research Governance Policy. The Health Equality Impact Assessment completed for the policy found there to be no impact.

### Health Impact Assessment

A Health Impact Assessment (HEIA) has not been completed as this was considered unnecessary.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	3 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

<b>Documents to read alongside this Procedure</b>	<ol style="list-style-type: none"> <li>1. Research Governance Policy (UHB 099)</li> <li>2. The UK Policy Framework for Health and Social Care Research (2017)</li> <li>3. Applying for JRO Sponsorship Low Medium Risk Studies SOP</li> <li>4. Applying for JRO Sponsorship Higher Risk Studies SOP</li> <li>5. JRO Modification Checklist</li> </ol>
<b>Approved by</b>	Joint Research Governance Group
<b>Accountable Executive or Clinical Board Director</b>	Medical Director
<b>Author(s)</b>	JRO Research Governance Team
<p><b><u>Disclaimer</u></b></p> <p><b>If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the <a href="#">Governance Directorate</a>.</b></p>	

<b>Summary of reviews/amendments</b>			
<b>Version Number</b>	<b>Date of Review Approved</b>	<b>Date Published</b>	<b>Summary of Amendments</b>
1.0	30/01/25	25/04/2025	Major updates implemented to reflect the formation of the JRO and the alignment of the Amendment draft and submission processes for both CAVUHB and Cardiff University. This SOP replaces all previous relevant CAVUHB and CU SOPs.
2.0	15/04/2026	17/04/2026	Major updates to reflect the updates to the new Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 and ICH GCP E6(R3). Major updates to reflect the implementation and use of the HRA's new Plan and Manage Health and Care Research system for preparing and submitting modifications.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	4 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## TABLE OF CONTENTS

<b>1.</b>	<b>DEFINITIONS/ABBREVIATIONS .....</b>	<b>5</b>
<b>2.</b>	<b>PREPARING A MODIFICATION .....</b>	<b>6</b>
<b>3.</b>	<b>SUBMITTING A MODIFICATION .....</b>	<b>8</b>
<b>4.</b>	<b>VALDATION CHECKS .....</b>	<b>9</b>
<b>5.</b>	<b>NOTIFYING NHS SITE R&amp;D OFFICES .....</b>	<b>10</b>
<b>6.</b>	<b>RECEIVING APPROVAL FOR A MODIFICATION .....</b>	<b>10</b>
<b>7.</b>	<b>ALTERING A MODIFICATION FOLLOWING REC/HRA/MHRA REVIEW .....</b>	<b>11</b>
<b>8.</b>	<b>IMPLEMENTATION OF MODIFICATIONS .....</b>	<b>12</b>
<b>9.</b>	<b>URGENT SAFETY MEASURES (USMS) .....</b>	<b>13</b>
<b>10.</b>	<b>TRAINING .....</b>	<b>14</b>
<b>11.</b>	<b>IMPLEMENTATION .....</b>	<b>14</b>
<b>12.</b>	<b>EQUALITY.....</b>	<b>14</b>
<b>13.</b>	<b>REVIEW .....</b>	<b>14</b>
<b>14.</b>	<b>USEFUL REFERENCES .....</b>	<b>14</b>
<b>15.</b>	<b>FREQUENTLY ASKD QUESTIONS .....</b>	<b>15</b>
<b>16.</b>	<b>APPENDICES .....</b>	<b>17</b>

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	5 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 1. DEFINITIONS/ABBREVIATIONS

ARSAC	Administration of Radioactive Substances Advisory Committee
CAG	Confidentiality Advisory Group
C&C	Capacity & Capability
CAVUHB	Cardiff and Vale University Health Board
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CU	Cardiff University
CWOW	Combined Ways of Working
GCP	Good Clinical Practice
HCRW	Health and Care Research Wales (equivalent to the HRA in England for Wales)
HMPPS	His Majesty's Prison and Probation Service
HRA	Health Research Authority
HSC	Health and Social Care (Northern Ireland)
IB	Investigator's Brochure
IRAS	Integrated Research Applications System
JRO	Joint Research Office
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR CRN	National Institute for Health and Care Research Clinical Research Network
R&D	Research & Development
RAF	Risk Assessment Form
RDB	Research Database
REC	Research Ethics Committee
RTB	Research Tissue Bank

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	6 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USM	Urgent Safety Measure

Modifications to a project approval can be categorised into substantial modifications, modifications of an important detail, and minor modifications.

1) For CTIMPs, substantial modifications can be further categorised as Route A or Route 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 defined in [regulation 11B of the Clinical Trial Regulations](#) and examples can be found in Appendix 1 of this SOP.

2) Modifications of an important detail 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 on completion of the modification tool.

3) Minor modifications may be implemented at any time and without informing the licensing authority or ethics committee at the point of implementation. Please note, other approvals may be required. This will be determined when completing the modification tool.

## 2. PREPARING A MODIFICATION

The CI (or delegate) should liaise with the Sponsor in a timely manner to discuss potential modifications and to determine their classification using a risk-based approach.

The MHRA may review the classification and rationale during a Good Clinical Practice (GCP) inspection.

### 2.1 Drafting study documents

Any modifications to a research study should be appropriately recorded in a Study Modification Summary Log. The Sponsor representative will be able to provide a template Study Modification Summary Log on request.

When modifying existing study documents, all changes should be made with track-changes enabled so that document reviewers can clearly identify any alterations. The document version number and date should also be updated in line with the JRO Information Sheet for Study Document Version Control.

Documents should be saved as clean and track changed versions.

When drafting new study documentation, the documents should be named appropriately and include a version number and date. The document version number and date should be allocated in line with the JRO Information Sheet for Study Document Version Control.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	7 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

New study documents should be saved for submission as clean versions.

If the CI or delegated member of the research team have any questions about how a modification should be presented for submission e.g., online surveys, advice may be sought from the Sponsor representative.

Where a Route B substantial modification to a CTIMP involves a change to any quality documentation (i.e. the IMP dossier, the Good Manufacturing Practice (GMP) documentation or the labelling documents), applicants should make this clear in the cover letter. The licensing authority will use this information to determine whether to exercise its right to undertake a full review of a Route B substantial modification before issuing a decision.

## 2.2 Completing the modification tool

The modification tool is used to categorise each change to a study and to identify which review bodies need to be notified. Depending on the organisation or modification type, the tool may be completed either as a standalone document or directly within the Plan and Manage Health and Care Research submission system. The study Sponsor will advise whether an amendment is eligible for the Plan and Manage Health and Care Research system and provide separate instructions. In both formats, the CI or delegated team member should enter each change separately, following the on-screen guidance and using the available drop-down options. Up to 10 different types of change can be entered in a single submission.

Before completing the tool, the CI (or delegate) should liaise with any relevant support departments or third parties if the proposed changes affect their involvement. Evidence of continued support and confirmation of adequate funding must be in place before Sponsor authorisation can be granted.

Once all changes have been entered, the tool will automatically generate the modification type and categorisation based on the information provided. If a change meets the definition of a Route B substantial modification to a CTIMP, it may be eligible for automatic approval by the licensing authority, and the justification for this must be clearly documented. For CTIMPs and other studies under the UK Clinical Trials Regulations, an MHRA fee applies to each amendment, and a Purchase Order number must be included at submission.

For JRO sponsored studies, the CI is **not** authorised to sign off or lock the modification tool. Sponsor sign off must be requested by email via the usual routes. The Sponsor representative will review the completed tool, ensure the categorisation is correct, and confirm that the changes align with the revised study documents.

For CTIMP modifications deemed substantial, the Sponsor will determine whether the change is a Route A or Route B substantial modification and whether MHRA notification is required. The CI (or delegate) must consult the Sponsor before any submission. For CTIMPs, the JRO modification checklist should also be completed and provided to the Sponsor.

For CAVUHB sponsored studies, the R&D Office will lead on reviewing the modification and assessing any implications for Capacity and Capability. Contractual changes will be arranged as needed, and the sponsorship risk assessment will be updated where appropriate.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	8 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

No modification may be submitted without prior Sponsor authorisation. Once the Sponsor representative has reviewed and approved the modification, the system will either generate a locked PDF version of the completed tool for submission or, where the modification tool is integrated into the submission system, Sponsor authorisation will trigger automatic submission to the appropriate review bodies.

### 3. SUBMITTING A MODIFICATION

The method for submitting the modification to the review body(ies) from whom you have received approvals (e.g. MHRA, HRA and HCRW Approval or REC favourable opinion) is dependent on the organisation and modification type.

Where a modification is eligible to be drafted directly in the Plan and Manage Health and Care Research Service, Sponsor authorisation will automatically trigger submission of modification.

Modifications for both non-CTIMPs and CTIMPs started before January 2022, and not eligible for submission via the Plan and Manage Health and Care Research Service, should be submitted via the [IRAS submission portal](#). The CI/authorised delegate should follow the on-screen instructions to submit the modification.

For clinical trials authorised via the combined review process (post January 2022) you should prepare and submit any modifications using [new part of the Integrated Research Application System in IRAS](#). A step by step guide to using the system for combined review can be found [here](#).

Upon submission the CI/delegated member of the research team will receive an automated email to confirm submission of the modification. The modification will be shared with REC and/or the HRA/HCRW for study-wide review as applicable.

For modifications, that require MHRA review, researchers should refer to the relevant CTU SOP for details on how to submit their modification to the MHRA.

#### 3.1 Submitting a modification of an important detail

Instructions for submitting a modification of an important detail are provided on completion of the modification tool.

For CTIMPs, the CI (or authorised delegate) will need to notify the authorities of the date on which the first participant was recruited to a clinical trial through the modification of an important detail process. This demonstrates that the trial has been registered in a public registry within the applicable deadline and [supports the licensing authority in monitoring the trial's approval status](#).

#### 3.2 Modifications to a Medical Device Trial

MHRA Devices must be notified of all proposed changes to the investigation (not only those classified as substantial modifications for the purposes of ethical review). A letter of no objection from MHRA Devices must be received before implementation. This includes changes made at the request of the REC. You can find more information regarding the process of submitting modifications to a medical device trial [here](#).

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	9 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

### 3.3 Submitting amendments to the Confidentiality Advisory Group (CAG)

For projects that required CAG approval, CAG should be notified of all amendments to the information provided in your original application. This is because support to process confidential patient information without consent is based on the precise details originally provided to CAG and so any change will **not** be covered by the existing support until a formal amendment is made and the amendment is supported.

You can find more information regarding the process for submitting an amendment to CAG approval [here](#). The possible outcomes of the review of the amendment are:

- Fully supported
- Conditionally supported
- Not supported

### 3.4 Substantial Amendments- Research Tissue Banks and Research Databases submission

- i. Research Tissue Banks (RTBs) and Research Databases (RDBs) do not need to complete the amendment tool for substantial amendments but instead continue to use the Notice of Substantial Amendment Form generated in IRAS.
- ii. Non-substantial amendments for RTB and RDB projects do not need to be notified to the REC.
- iii. 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.

More information can be found [here](#).

Please also note that for studies which required approval from other regulatory bodies for example: Confidentiality Advisory Group (CAG), His Majesty's Prison and Probation Service (HMPPS) and Administration of Radioactive Substances Advisory Committee (ARSAC) or if you are including involvement of adults lacking capacity for the first time, or extending involvement of adults lacking capacity to a new nation, please refer to [IRAS](#) for submissions requirements.

## 4. VALIDATION CHECKS

Once submitted, the application undergoes validation checks to ensure that all documentation required for the application to be reviewed has been included.

The outcome of these checks will be communicated by email or via the relevant submission system within 7 calendar days of submission. As soon as possible during this 7-day period, the applicant will be notified of any deficiencies identified during the validation checks and allow them to be addressed. If these deficiencies remain unresolved by the end of the 7 days, the application will be invalidated, and the applicant will need to resubmit the application with the deficiencies corrected.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	10 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 5. NOTIFYING NHS R&D OFFICES

Once in receipt of confirmation that the modification submission is valid, the CI (or authorised delegate) should notify NHS R&D offices of the modification:

**For multi-centre studies involving NHS organisations in England and/or Wales**, the CI (or delegate) should share the completed Modification Tool with confirmation of modification category and, if applicable, updated documents together with relevant participating NHS organisations.

In doing so, you should include the NHS R&D Office, Local Clinical Research Network (LCRN) (where applicable) as well as the local research team.

A template email to notify participating NHS organisations in England and/or Wales is provided on the [IRAS Help webpage](#).

**For multi-centre studies involving NHS organisations in Scotland and/or Northern Ireland**, the coordinating function of the lead nation will, upon categorisation, share the modification with the coordinating function of any other participating nation(s). (HRA, HCRW, NHS Research Scotland Permissions Co-ordinating Centre and Northern Ireland CRN Co-ordination Centre, respectively). There is no need to separately submit to each of these nations.

However, the CI or delegate should share these documents upon receipt of the categorisation email with the research teams at relevant participating NHS/HSC organisations in Northern Ireland and/or Scotland who should prepare to implement the modification.

- i. Each participating organisation should review the modification in parallel to HRA/HCRW, REC and MHRA review (as appropriate) and put in place the necessary arrangements, as required, for continued local C&C to deliver the study.
- ii. The CI (or delegate) should promptly relay the REC, HRA/HCRW, and MHRA (as required) modification review outcomes to the participating organisation Investigators /R&D Office (and LCRNs as appropriate) as they become available.
- iii. It is the CI's (or delegate) responsibility to retain all modification correspondence with REC, HRA/HCRW and participating organisations within the TMF.

## 6. RECEIVING APPROVAL FOR A MODIFICATION

For substantial modifications to a non-CTIMP submitted to the REC, you should await email communication from the REC with the outcome of their review before implementing the change. Depending on the study design, you may also require confirmation of HRA/HCRW approval of the modification before implementation.

Where a HRA review is required, they may review the amendment and issue Approval of the amendment separately to the REC.

An outcome will be issued within 35 calendar days of the submission being confirmed as valid.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	11 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

There are 4 possible outcomes from the initial REC review of a substantial modification request. These are:

- favourable opinion
- favourable opinion subject to conditions
- unable to issue a favourable opinion and requests further information
- unfavourable opinion

For Route B substantial modifications to a CTIMP, see the guidance on [Automatic approval of Route B substantial modifications by the licensing authority](#).

Valid applications for Route A substantial modifications to a CTIMP are reviewed by the licensing authority or the ethics committee (“the authorities”), or both, depending on the nature of the modification. A joint decision will be issued by email (and through IRAS, for trials approved through combined review) within 35 calendar days of the validation date. A combined decision will be issued even if only one authority has reviewed the application. The initial decision will be one of the following:

- the authorities approve the proposed modification
- the authorities approve the proposed modification subject to conditions
- the authorities do not approve the proposed modification, setting out the grounds for this decision

If a modification is approved subject to conditions, the notice will specify what actions the must be taken to meet those conditions. The substantial modification is considered approved only if all conditions are satisfied. A record of how the conditions have been met should be kept in the TMF, but it is not necessary to inform the authorities that the conditions have been met before implementing the modification, unless otherwise specified in the approval letter.

All approval email correspondence should be filed in the TMF.

## **7. ALTERING A MODIFICATION FOLLOWING REC/HRA/MHRA REVIEW**

The introduction of the request for information process removes the option to submit a modified amendment. Instead, the option to provide further detail to the REC/HRA/MHRA will be provided before a final decision is given.

Modified amendments must not be submitted.

The applicant will be given one opportunity to provide further information and have the application reconsidered. The additional information needed will be specified in the notice stating that the application has not been approved, and it will be made clear whether the additional information requested relates to the ethics committee’s opinion, or for CTIMPS, the licensing authority’s decision, or both.

The notice will outline the timeframe within which applicants must submit the requested further information (through IRAS for combined review trials or by email to the relevant authority for non-combined review trials), either as a written response or an amended

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	12 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

application for approval, for the application to be reconsidered. The application will be treated as rejected if this deadline is not met.

In instances where an amended application is required, a new modification tool should be completed, indicating that it relates to a revised modification at the relevant question.

A decision will be issued by email (and through IRAS, for trials approved through combined review), within 10 calendar days of the response being submitted, stating that the application is either approved, approved with conditions, or not approved. If the application is still not approved, the reasons will be outlined and the application will be treated as rejected. No further amendments to the application will be considered, and a new application will need to be submitted (including the full MHRA application fee for modifications to CTIMPs).

## 8. IMPLEMENTATION OF MODIFICATIONS

There can be presumed implementation following regulatory approval, unless an NHS organisation raises an objection to the modification or requests an extension to the review period. The cover email accompanying submission to NHS R&D should advise of the planned implementation date in the absence of either of these (usually immediate for non-substantial modifications). In all cases, the CI (or delegate), must ensure that modifications and any finalised approved supporting documentation are passed to the local Investigators and their research teams at all organisations.

When no acknowledgement is sent by R&D within 35 days of the modification being shared, researchers are strongly advised to contact the relevant R&D office(s) prior to implementing substantial modifications.

A modification concerning the addition of a new participating organisation can be implemented once favourable REC and HRA and HCRW approvals are in place and the NHS organisation has confirmed C&C. For higher risk clinical trials (including, but not limited to CTIMPs), the Sponsor/delegate will also need to have issued 'Green Light' to the new participating organisation, upon successful completion of all Initiation processes (as outlined in the Trial Protocol).

### *i. Confirming implementation of all modifications - for participating organisations in England and/or Wales only:*

Use the [template email to notify participating organisations in England and Wales](#) that a modification can be implemented. The template email helps you to be clear and consistent when informing participating organisations. Send the email to the R&D office, local research team, and (for participating organisations in England) the LCRN for studies included on the NIHR CRN portfolio.

### *ii. Confirming implementation of all modifications - for participating organisations in Scotland and/or Northern Ireland only:*

Tell the local research team when you want to implement the modification at their organisation. You can use the email template for England and Wales to help you do this.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	13 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 9. URGENT SAFETY MEASURES (USMS)

Substantial modifications normally require prior approval from the licensing authority and ethics committee. The only exception is when changes are implemented as Urgent Safety Measures (USMs) to address an immediate hazard to participant health or safety.

### i. Taking a USM

The Sponsor, CI, or NHS Investigator may implement USMs without prior approval when necessary to protect participants (e.g., unexpected deaths at a participating organisation requiring suspension of recruitment, or a pattern of SAEs/SUSARs requiring immediate action across participating organisations).

### ii. Immediate Notifications

REC, HCRW/HRA, the MHRA (for CTIMPs), and the R&D office must be notified **immediately**, and **no later than 3 days** after the USM is taken. The notification must include details of the measure and its rationale.

### iii. Additional MHRA Requirements for CTIMPs

- The MHRA Clinical Trials Unit must be contacted by phone (020 3080 6456) ideally within **24 hours**.
- If phone reporting is not possible, email [clintrialhelpline@mhra.gov.uk](mailto:clintrialhelpline@mhra.gov.uk) with contact details, IRAS ID/EudraCT number, a description of the USM, and the reason phone reporting was not possible.
- For trials **not** approved via Combined Review, written notification should be emailed to the medical assessor.
- For trials **approved via Combined Review**, written notification must be submitted through the **IRAS CWOW** system.
- Regardless of the initial discussion, the sponsor must submit written notification to the licensing authority describing the events, actions taken, and any further actions requested.
- Under Regulation 30, this must be submitted within **7 calendar days** of implementing the USM (or as soon as possible during a pandemic posing serious risk to human health).

### iv. Internal Governance

The CI or delegate must liaise with the JRO Research Governance Team throughout the process.

### v. Sponsor Procedures

Sponsor safety reporting procedures must be followed.

### vi. Subsequent Amendments

If the USM results in a substantial amendment to the protocol or documentation, a substantial amendment must be prepared and submitted within **2 weeks** of first notifying the licensing authority by phone.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	14 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 10. TRAINING

Education and support should be available from the Sponsor and HCRW Support & Delivery Centre for Researchers who are involved in conducting clinical research studies. Sponsor office staff should receive relevant training (internal and external as necessary) to ensure that national procedures are adhered to in the review and management of modifications.

## 11. IMPLEMENTATION

The Clinical Board R&D Leads can facilitate implementation by ensuring that all relevant research active personnel within their Boards and University Schools are aware of the procedure and the implications for their practice. The CU Research Governance Team will be responsible for ensuring that relevant University researchers and departments are made aware of this SOP.

## 12. EQUALITY

An equality impact assessment has been carried out on the Research Governance Policy, under which this Procedure falls. No adverse impact has been identified.

## 13. REVIEW

The Procedure should be reviewed every 3 years, or more regularly if important new legislation so requires.

## 14. USEFUL REFERENCES

[The Medicines for Human Use \(Clinical Trials\) Regulations 2025, \(SI 2025 No. 538\) and subsequent amendments.](#)

[The UK Policy Framework for Health and Social Care Research \(2017\)](#)

Research Governance Policy (UHB 099)

Applying for JRO Sponsorship Low Medium Risk Studies SOP

Applying for JRO Sponsorship Higher Risk Studies SOP

JRO Modification Checklist

JRO Information Sheet for Study Document Version Control

[Amending an approval - Health Research Authority \(hra.nhs.uk\)](#)

[Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#)

[IRAS Help - Maintaining your approvals - Amendments \(myresearchproject.org.uk\)](#)

[IRAS Help - Maintaining your approvals - Amendments for projects conducted in NHS/HSC \(myresearchproject.org.uk\)](#)

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	15 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 15. FREQUENTLY ASKED QUESTIONS

**Q: How long does it take for an modification to be reviewed?**

A: The length of time it takes for the Sponsor to review and authorise a modification varies and will depend on the complexity of the changes and the capacity within the JRO Research Governance team at any given time.

Some modifications do not require review by a REC, for example, where a change only includes the addition of a new NHS organisations carrying out the same activities as other approved organisations. In these instances, on submission of the modification via the IRAS gateway, the researcher will receive an automated email response confirming immediate approval of the change.

Where approval from the REC/MHRA is required for the modification, an opinion should be given in all cases within 35 calendar days of receiving a valid notice of modification. The 35-day clock applies to review of all substantial modifications, except those proposing to include adults lacking capacity for the first time in a non-CTIMP, where 60 calendar days is allowed for the review and the clock may be stopped once to request further information or clarification.

**Q: If a substantial modification needs to be submitted to an approved study prepared in IRAS, do I make any updates to the REC form or project dataset if these are affected, or do we just submit the modification tool as usual?**

A: Where substantial modifications are required following ethical approval, please follow the guidance in sections 2-7 of this document or refer to the [IRAS Help](#) guidance. At your discretion you may submit a further version of the form from IRAS in support of this, however, this is usually discouraged and not normally required.

**Q: What if I make a change to my study which introduces the need for NHS REC review for the first time?**

A: If your study previously had HRA/HCRW Approval but did not require NHS REC review (e.g. it was limited to the collection of routinely-gathered, anonymous NHS data or only involved the recruitment of NHS staff) and you now need to make a change which requires NHS REC review (e.g. you now wish to contact patients and involve them in an interview), then this cannot be submitted as a Substantial modification. Instead, please seek advice from the HRA- [amendments@hra.nhs.uk](mailto:amendments@hra.nhs.uk) and copy in the relevant Sponsor team to your email.

**Q: The modification tool provides an option for either the CI or Sponsor to sign it off. Therefore, as CI (or delegate) can I sign it off, and submit the modification without contacting the JRO Research Governance team?**

A: For studies Sponsored by a Cardiff JRO organisation, the authority to sign off the modification tool **has NOT** been delegated to the CI, therefore the Sponsor representative **MUST** sign the modification tool.

Sponsor electronic sign-off of the modification tool for all amendment types must be requested by the CI (or delegate).

**Q: How should I keep track of the modifications I have made to my study?**

A: It is good practice to keep a study modification log to record the changes you make to a study. A modification log records information including the modification reference, brief

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	16 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

details of the changes with references to the relevant study documentation, and key dates related to the modification such as date of submission to REC and/or the HRA/HCRW, and date the approval was received. The JRO Research Governance team can provide a template modification log for your study.

**Q: What is version control, and how do I maintain good version control in my study?**

Version control is the process by which different drafts and versions of a document or record are managed. Version control should be used where more than one version of a document exists, or where this is likely to be the case in the future. It is good practice to keep a version control log. This is a table that provides further details of what changes were made to a document, when, and by whom. A version control log can be added at the beginning or end of the document itself, or created as a separate document, and stored in the study master file.

The version control table should be updated each time a change is made to the document. It details:

- The new version number;
- The date of the change.
- The person making the change;
- Details outlining the change itself and/or it's purpose;

For more information on how to manage version control and for a template that you may use, please refer to the JRO Information Sheet for Study Document Version Control.

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	17 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

## 16. APPENDICES

Appendix 1: Definitions and examples of Substantial modifications, modifications of an important detail and minor modifications

Please note examples included in this table should not be considered an exhaustive list.

<p><b><u>Substantial modifications</u></b></p>	<p><b><u>Examples</u></b></p> <ul style="list-style-type: none"> <li>• <u>Temporary halt of the trial or temporary halt at a trial location within the UK</u></li> <li>• <u>Re-start of the trial following a temporary halt</u></li> <li>• <u>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)</u></li> <li>• <u>Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial</u></li> <li>• <u>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</u></li> <li>• <u>Change of the chief investigator</u></li> </ul>
<p><b><u>Substantial modifications Route A</u></b>  Substantial modifications that are likely to have a substantial impact on:</p> <ul style="list-style-type: none"> <li>• the safety or rights of the participants</li> <li>• the reliability or robustness of the data generated in the trial</li> </ul>	<p><b><u>Examples</u></b></p> <ul style="list-style-type: none"> <li>• Changes to primary or secondary endpoints that have a significant impact on the safety or scientific value of the clinical trial</li> <li>• Changes to Investigational Medicinal Product(s) (IMP) (e.g. using a different IMP or changing the IMP's formulation) – applies to traditional design and complex innovative design trials (basket, umbrella or platform trials, and other adaptive designs)</li> <li>• Addition of a trial arm or placebo group</li> <li>• Significant change in the absolute number of trial participants</li> </ul>

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	18 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

	<ul style="list-style-type: none"> <li>• Changes to the assessments that form the participant safety monitoring visits</li> <li>• The addition of new toxicological or pharmacological data or a new interpretation of the data that is relevant to investigators and protocol changes are required from a safety perspective</li> <li>• Changes to the reference safety information (RSI) involving a decrease in frequencies</li> <li>• Change to the approved IMP labelling</li> <li>• Notification of a temporary halt to all or part of a trial</li> <li>• Request to restart a trial following a prior temporary halt (even if no protocol update is required)</li> </ul>
<p><b><u>Substantial modifications Route B</u></b> The definition can be found in regulation <a href="#">11B of the Clinical Trial Regulations</a></p>	<p><b><u>Examples</u></b></p> <ul style="list-style-type: none"> <li>• A change to the primary objective of the clinical trial</li> <li>• Use of new measurements for the primary endpoint</li> <li>• Changes to the trial design which have a significant impact on statistical consideration</li> <li>• Changes in the definition of the end of the trial (except a change to the planned end date, which is minor)</li> <li>• In trials involving an IMP authorised for use in the UK and used according to that authorisation, a change to the number of planned interactions with the participants to assess their ongoing safety in the trial, unless the change is in response to a new safety concern (which is a Route A substantial modification)</li> <li>• Changes to the list of concomitant medications that the participant can or cannot take</li> <li>• Inclusion of a UK-specific addendum or protocol into a global protocol version, unless the addendum or protocol results in a change to approved safety reporting</li> </ul>
<p><b>Modifications of an important detail</b></p>	<p><b><u>Examples</u></b></p> <ul style="list-style-type: none"> <li>• Changes to the trial identification (for example the trial title)</li> </ul>

Document Title: <i>Managing Modifications for Cardiff JRO Sponsored Research</i>	19 of 19	Approval Date: 15/04/2026
Reference Number: SOP/003/06		Next Review Date: 15/04/2029
Version Number: 2		Date of Publication: 17/04/2029
Approved By: Joint Research Governance Group		

	<ul style="list-style-type: none"> <li>• Submitting the date that the first UK trial participant is recruited (CTIMPs)</li> <li>• 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</li> <li>• Change to contact details for named contacts for the trial, for example the sponsor, sponsor representative or chief investigator</li> <li>• Change of investigator (other than the chief investigator) at a trial location in a multi-centre trial (CTIMPs)</li> <li>• Addition of new trial locations not listed with the original request for authorisation and REC application where there are no additional documents for submission (CTIMPs)</li> <li>• Change of the sponsor's legal representative</li> <li>• Change of the sponsor</li> </ul>
<p><b>Minor Modifications</b> A change that does not materially affect participant safety, rights, trial integrity, or data reliability.</p>	<p><b><u>Examples</u></b></p> <ul style="list-style-type: none"> <li>• Addition of a new organisations and/or investigator (non CTIMPs)</li> <li>• Changes in the number of participants per trial location, if any change is insignificant in view of the absolute number of participants</li> <li>• Changes in the processes associated with record keeping used by the research team for recording trial data</li> <li>• Internal changes to the sponsor's organisation</li> <li>• Changes in the logistical arrangements for storing or transporting samples</li> <li>• Changes in technical equipment</li> <li>• Minor changes to the protocol or other study documentation, for example correcting errors, updating contact points, minor clarifications</li> </ul>