

Research Governance  
and Integrity Team

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## Modifications to Healthcare Research

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Version 1.0	03 Jul 2006	Change in substantial amendment form
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Version 14.0	27 Apr 2026	Updates to SOP following Legislative changes

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## 1. PURPOSE

This SOP describes the procedure for making Modifications to CTIMPs and Non-CTIMPs to the Health Research Authority (HRA), the NHS Research Ethics Committee (REC) and the Medicines and Healthcare products Regulatory Agency (MHRA). Other bodies that may need to approve or be notified of modifications include the National Health Service (NHS) / Health and Social Care (HSC) Research and Development, Administration of Radioactive Substances Advising Committee (ARSAC), Confidentiality Advisory Group (CAG) and HM Prison and Probation Service (HMPPS).

Modifications to additional or alternative REC committees may need to be submitted to dedicated REC committees such as [Ministry of Defence Research Ethics Committee - GOV.UK](#) (cited on 11 March 2026).

## 2. INTRODUCTION

Modifications are changes made to a research study after favourable ethical opinion or approval by a regulatory body has been given. A clinical trial approval may be modified by the trial's sponsor, the licensing authority, or the ethics committee. They can be made to a protocol, other essential documentation or other aspects of a study's arrangements. All research protocols or other essential documents should have clear version numbers and dates in order to maintain accurate records and audit trails. Any modifications to a research protocol or other essential documents should have a concordant changes made to the date and version recorded on these documents.

### 2.1. CTIMP Modification(s) Definitions

A modification to a research project classified as a CTIMP can be defined as the following: a **Substantial Modification**, a **Modification of an important detail** or a **Minor Modification**.

**Substantial Modifications** are categorised into two routes:

**Route A:** 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:** A modification 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 but where there are no new significant safety concerns with any of the investigational medicinal products, as far as the sponsor is aware having made reasonable enquiries; and which meets either Condition A, Condition B or Condition C (see figure below). For further details on the conditions, please see the following link: [The Medicines for Human Use \(Clinical Trials\) \(Amendment\) Regulations 2025](#) (cited on 11 March 2026). The justification for the decision of a route B modification should be clearly documented by the sponsor.

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Condition A	Condition B	Condition C
<ul style="list-style-type: none"> <li>• Not a FIH Trial</li> <li>• Modification assessed and approved in the:               <ul style="list-style-type: none"> <li>• European Union</li> <li>• an EEA State</li> <li>• United States of America</li> </ul> </li> <li>• Same documents</li> </ul>	<ul style="list-style-type: none"> <li>• Specified Protocol Changes</li> <li>• Examples:               <ul style="list-style-type: none"> <li>• a change to the list of concomitant medication</li> <li>• new measurement(s) for the primary endpoint</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Specified IB/SmPC Changes</li> <li>• Example:               <ul style="list-style-type: none"> <li>• inclusion of new toxicological or pharmacological data (with no safety concerns)</li> </ul> </li> </ul>

For examples of Route A Substantial Modifications (**including changes to Reference Safety Information documents**), please refer to the following link: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (cited 11 March 2026) or [Update to 'amendment' terminology - Health Research Authority](#) (cited 11 March 2026).

For examples of Route B substantial modifications, please refer to the following link: [Tab1. Route B substantial modifications.pdf](#) (cited 11 March 2026).

Please also see the decision tree for determining the correct category for a modification via the following link: [Fig1. Modification types.pdf](#) (cited 11 March 2026).

**Modifications of an Important Detail** do not significantly impact the safety or rights of 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.

For examples of Modifications of an Important Detail, please refer to the following link: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (cited 11 March 2026).

**Minor modifications** can be defined as a change to the details of a study which have no significant implications for participants or the conduct, management or scientific value of the study. Minor modifications may be implemented at any time and without informing the licensing authority or ethics committee at the point of implementation (however, other approvals may be required (for example HRA approval), which can be determined using the modification tool). The sponsor must keep records of any modifications implemented and, if requested, make them available to the licensing authority or ethics committee.

For examples of minor modifications, please refer to the following link: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (cited 11 March 2026) or [Update to 'amendment' terminology - Health Research Authority](#) (cited 11 March 2026).

Classification of a modification will depend on the output of the modification tool. To ensure the correct output is generated, the tool should be completed with reference to any accompanying guidance notes and definitions provided within the tool (e.g. glossary of modification options tab) and relevant MHRA/HRA guidance.

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## 2.2. Non-CTIMP Modification(s) Definitions

As per [Update to 'amendment' terminology for non-CTIMPs - Health Research Authority](#) (cited 11 March 2026), from 28 April 2026, the term 'amendment' for changes to approved non-CTIMP studies will no longer be used. Instead, they'll be referred to as 'modifications'.

This is to align with changes to CTIMPs when [updated clinical trials regulations](#) (cited 11 March 2026) come into effect on 28 April 2026 and to promote consistency across all UK clinical research.

This change will apply to all non-CTIMPs except for research tissue banks (RTBs) and research databases (RDBs), where the 'notice of substantial amendment' form will still be used and the 'Amendment' tab in the [Integrated Research Application System \(IRAS\)](#) (cited 11 March 2026) will remain for submission.

Modifications for non-CTIMPs will be categorised as:

**Substantial Modifications:** Substantial modifications are considered to be a modification to 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 research study. Substantial modifications may also need other approvals, for example Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval, depending on the modification.

**Modification of an important detail:** A new category of modification will be introduced, known as 'modification of an important detail'. This is a modification that does not significantly impact participant safety or rights, which the Research Ethics Committee (REC) only need to be made aware of for administrative or oversight purposes. These types of modification are not reviewed by the REC, and no outcome will be issued. They are for information only. These modifications may however need other approvals (for example HRA and HCRW approval).

**Minor Modifications:** The term 'minor modification' replaces the term 'non-substantial amendment' and describes changes that do not fall into the category of 'substantial modification' or 'modification of an important detail'. These can be implemented at any time without informing the REC, although other approvals (for example HRA and HCRW Approval) may be required.

**Examples of modifications for each category** can be found at [Update to 'amendment' terminology for non-CTIMPs - Health Research Authority](#) (cited 11 March 2026).

The classification of a modification will depend on the output of the modification tool. To ensure the correct output is generated, the tool should be completed with reference to the **glossary of modification options tab** on the modification tool.

Research Governance  
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The HRA has begun rolling out a new digital service, plan and manage health and care research. Initially in private beta, it is available only to invited sponsors and eligible studies (e.g. single-nation, non-NHS REC studies) and will expand over time. This service is intended to eventually replace the traditional CWOW/IRAS/Modification Tool submission process.

Imperial College London and Imperial College Healthcare NHS Trust are participating in the early roll-out for eligible studies. Other study categories will join at a later stage.

Researchers and sponsors should submit modifications for eligible studies using the new service. This process replaces the traditional amendment/modification Tool, with all required information entered directly into the system. All other studies, including those not yet eligible for the service, should continue to use the standard modification process.

Eligibility and guidance for the digital service have been communicated to researchers. To request these resources (including setup instructions and links to HRA documentation) please contact [RGIT@imperial.ac.uk](mailto:RGIT@imperial.ac.uk).

**3. PROCEDURES**

For all studies (CTIMP & Non-CTIMP), it is the responsibility of the sponsor to assess the category for which a modification constitutes (please see above).

For CTIMP modifications deemed substantial, it is the sponsor's responsibility to determine whether it meets the definition of a Route B substantial modification and thus is eligible for automatic approval by the licensing authority. **The justification for this decision should be clearly documented.** A modification is considered a Route B substantial modification (and therefore eligible for automatic approval from the licensing authority) based solely on the nature of the modification itself and is independent of whether the trial was authorised via automatic authorisation (i.e. notifiable trials). [Clinical trials for medicines: notifiable trials - GOV.UK](#) (Cited 11 March 2026).

For Imperial College AHSC sponsored studies, if a modification is required and the Chief Investigator, Principal Investigator or any member of the study team assigned by the investigator to initiate study modifications, is not sure what category the proposed study modification should be, then the Research Governance & Integrity Team (RGIT) expects the team to contact them via email with a brief description of the proposed change(s). For CTIMPs, please use the email: [rgit.ctimp.team@imperial.ac.uk](mailto:rgit.ctimp.team@imperial.ac.uk). For non-CTIMP studies, please use the email: [rgit@imperial.ac.uk](mailto:rgit@imperial.ac.uk).

Research Governance  
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An up-to-date version of the Modification Tool should be downloaded from the following link [IRAS Help - Maintaining your approvals - Amendments](#) (cited on 11 March 2026). The tool can also be obtained by contacting the licensing authority at [clintrialhelpline@mhra.gov.uk](mailto:clintrialhelpline@mhra.gov.uk), for trials not approved through combined review.

The information about your modification should be entered into the applicable sections of the tool. Please ensure that the list of documents to be submitted with the modification are included in the main summary section so that it is clear what the latest dates and versions of the documents will be. The modification tool will allow you to enter up to 10 changes per tool. If more changes are required for one modification, contact [amendments@hra.nhs.uk](mailto:amendments@hra.nhs.uk) for assistance.

Once completed, the tool and all applicable documentation, such as modified study documents (please see the following link for further information: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (Cited 12 March 2026) or cover letters (please see the following link for further guidance on what information should be included in the cover letter: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (Cited 11 March 2026) should be sent to the RGIT Team (email addresses listed in the section above) for review. The modified documents must show the previous and new wording in tracked changes so that the changes can be readily identified. The chief investigator or appointed member of the study team may also include other supporting information, such as a summary of trial data, an updated safety analysis or a report from a trial monitoring committee. Where the modification could significantly affect the scientific value of the research, further evidence of scientific and/or statistical review should be provided.

Once reviewed and all queries resolved, the RGIT reviewer will then lock the tool for submission. This will generate a locked pdf copy of the completed tool.

For CTIMPs a modification acknowledgment letter will then be sent to the study team who submitted the modification, along with the locked modification tool, approving the modification for submission.

All modifications will be authorised (or “locked”/signed, depending on the system) by a designated sponsor representative/delegate within RGIT.

For all project-based research (other than those specific projects selected for the HRA Digital Modification Service – see details above), the Modification tool is used for modifications. For Research Tissue Banks (RTBs) and Research Databases (RDBs) use the Notice of Substantial Modification Form generated in IRAS to notify substantial modifications to the REC.

For all types of research, modifications and supporting documentation should be uploaded and submitted for review via the online submission functionality.

### 3.2. Submission of a CTIMP Modification(s)

For trials approved through the combined review process (CWOV), Route A or Route B substantial modifications should be submitted via a single application (including all documentation) through the Integrated Research Application System (IRAS) where they will be passed on to the MHRA & REC (where applicable) for review. If the clinical trial was not originally approved through the combined review process, the modification will need to be submitted to both the licensing authority (via MHRA Submissions) and the ethics committee (via the online portal on IRAS). There are fees applicable to submission of a substantial modification (for further details, please see the following link: [Make a payment to MHRA - GOV.UK](#) (cited 11 March 2026)).

Submitting through CWOV can be done via 'My Projects' and the Project Details page by selecting 'New Modification'. From 'My Projects' the researcher will be able to create modifications for any projects with an 'approved' status. Click on the IRAS ID of the project and from the Project Details page, select 'New modification' in the top right-hand corner of the screen. Enter the Sponsor modification reference number, sponsor modification date, and select whether this is a substantial or modification. The modification number and date will populate directly into letters issued by the regulators and will ensure that it is the sponsor allocated modification number which appears on these documents.

This will activate a set of sub-questions as follows:

#### Substantial modification options:

- Chief Investigator (for amendments to change the CI)
- Sponsor Group (for amendments to change the sponsor or sponsor's legal rep)
- Administrative (if you are only changing the contact details for the CI, sponsor, sponsor contact or sponsor legal rep)
- Project information (for any other type of substantial amendment not covered by the above)

#### Non-substantial modification options:

- Non-substantial
- Non-substantial no study wide review required
- Extend study end date

**Important:** Certain modifications will need to be submitted separately. The following modification types cannot be combined with any other changes: 'Chief Investigator', 'Sponsor Group', 'Administrative' and 'Extend Study End Date'.

For example, to update a CI's contact details, an administrative modification should be submitted. Any other changes with the submission should not be included, and the change as part of a different amendment type should not be submitted.

When the modification form is complete, and all documentation uploaded, including the locked modification tool, then the form can be submitted. This will send the modification directly to the sponsor organisation for review and submission.

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The option chosen must match the information on the Modification Tool. If incorrect information is entered it may result in the modification being rejected and a new modification created and submitted.

**IT SHOULD BE NOTED THAT SELECTING ‘SUBSTANTIAL MODIFICATION – PROJECT INFORMATION’ WILL PROVIDE THE OPTION TO INDICATE WHETHER THE MODIFICATION RELATES TO AN URGENT SAFETY MEASURE.**

Once submitted, the application undergoes validation checks to ensure that all documentation required has been included. The outcome of these checks will be communicated by email (and through IRAS, for trials approved through combined review) within 7 calendar days of submission. As soon as possible during this 7-day period, the licensing authority may notify the applicant by email of any deficiencies identified during the validation checks and allow them to be addressed. If these deficiencies remain unresolved by the end of these 7 days, the application will be invalidated, and the applicant will need to resubmit the application with the deficiencies corrected.

Valid applications for **Route A substantial modifications** are reviewed by the licensing authority or the ethics committee, 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.
- authorities approve the proposed modification subject to conditions (see below).
- the authorities do not approve the proposed modification, setting out the grounds for this decision (see request for further information below).

In exceptional circumstances, the licensing authority or ethics committee may need to consult with a relevant committee or specialist group before issuing a decision on an application for a substantial modification.

There is also now a fast-track research ethics review service for all Phase 1 healthy volunteer studies regarding substantial modifications. For further information on this, please see the following link: [The approvals process for Phase 1 healthy volunteer trials - Health Research Authority](#) (cited 11 March 2026)

**If an application is approved subject to conditions**, the notice will specify what actions the sponsor must take to meet those conditions. The substantial modification is considered approved only if all conditions are satisfied. In most cases, the sponsor must ensure that the conditions are met before the substantial modification is implemented. The sponsor should keep records of how the conditions have been met, 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.

In some cases, the authorities may allow a condition of approval to be fulfilled at a specific timepoint after the modification is implemented. In these cases, the sponsor may implement the modification before meeting the condition, but failure to meet the condition by the specified timepoint will mean that the approval is not valid and

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implementation must be reversed. The licensing authority will assess compliance with any conditions attached to the approval of a substantial modification during inspection.

Where the authorities **do not approve** the proposed substantial modification, the applicant will be given one opportunity to provide further information and have the application reconsidered (request for further information). 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 licensing authority's decision, the ethics committee's opinion, or both.

Applicants have 60 calendar days from the date on which the decision letter was issued to 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 application for approval, in order for the application to be reconsidered. The application will be treated as rejected if this deadline is not met.

Extensions to this deadline can be requested by contacting the MHRA at [clintrialhelpline@mhra.gov.uk](mailto:clintrialhelpline@mhra.gov.uk) or contacting the ethics committee directly, if the information requested relates only to its decision, explaining why the extension is needed and proposing an alternative submission date.

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 modifications to the application will be considered (although the applicant can appeal this decision, as explained in the next section). If the applicant wishes to continue obtaining approval for the substantial modification, a new application will need to be submitted (including the full application fee).

**For Route B Modifications**, applications for approval should go through the same process as for a Route A with the same accompanying documents. The cover letter must include a statement that the application is for approval of a Route B substantial modification. Additional information should be also submitted as part of the full application:

- **Route B substantial modification:** All changes to a non-first-in-human trial have been reviewed and approved as part of a substantial amendment or modification in the EU, EEA, or USA, provided that the UK modification includes the same documents and does not include any UK-specific aspects.
- **Additional information:** Confirm in the submission the regulatory authority that has approved the modification based on the same documents and provide evidence of this approval (or, for the FDA, confirmation that after 30 calendar days there has been no notification of a clinical hold), the date of approval, and any conditions issued.

Once an application is determined to be valid, the applicant will receive confirmation by email that the Route B substantial modification application has been received by the licensing authority. The licensing authority will check the application against the eligibility criteria for Route B substantial modifications to determine whether it is appropriate to provide automatic approval. If the application meets the eligibility criteria:

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- Confirmation of automatic approval from the licensing authority will be issued by email within 14 calendar days of validation.
- The modification cannot be implemented unless a combined decision that the modification is approved (or approved with conditions) is received. As the ethics committee reviews Route B substantial modifications through the same process as Route A substantial modifications, the combined decision (which could be approval, approval with conditions, or not approved with a request for further information) will be issued within 35 calendar days of validation.
- Where no ethics committee opinion is needed, the notice of automatic approval will specify that this represents a joint decision from the licensing authority and ethics committee.

If the licensing authority finds that the application does not meet the eligibility criteria:

- The applicant will be issued with a letter stating this, and the reason for objection, via email within 14 calendar days of validation.
- The application will then automatically undergo review as a Route A substantial modification, with a combined decision issued within 35 calendar days of validation. The applicant does not need to resubmit their application or documentation.
- If the applicant does not want the application to undergo review as a Route A substantial modification, they may withdraw the application at this point and the application fee will be refunded.

The licensing authority reserves the right to undertake a full review before issuing a decision, even where the application is submitted as a Route B substantial modification. In such cases, the licensing authority will contact the sponsor to discuss this within 14 days of validation.

**Appeals:** If an application is not approved or the applicant disagrees with the conditions attached to the approval, they have 28 calendar days from receiving the decision to send written notice to [appeals@hra.nhs.uk](mailto:appeals@hra.nhs.uk) of their intention to appeal the licensing authority decision or ethics committee opinion (further details on appeals can be found on the following link: [Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#) (cited 11 March 2026).

**Withdrawing an application to make a substantial modification:** Applicants may withdraw their application to make a substantial modification at any time before a decision is issued or a request for further information is raised.

To withdraw an application:

- Guidance on withdrawing applications submitted via IRAS can be found in the Step-by-step guide to using IRAS for combined review.
- For applications made separately to the licensing authority and ethics committee, contact MHRA at [clintrialhelpline@mhra.gov.uk](mailto:clintrialhelpline@mhra.gov.uk) and contact the ethics committee by email.

Include a brief description of why the withdrawal request is being made. The applicant will receive an email (and, for combined review trials, a notification in IRAS) confirming that the application has been withdrawn. Depending on the proportion of the review that had been completed at the point of withdrawal, some of the application fee may be refunded. Re-submission of a modification as a substantial modification will be subject

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to the same approval process before implementation as described in section 4 of this SOP.

**Modification of an important detail:** Instructions for notifying the authorities about a modification of an important detail are provided on completion of the modification tool. No fees are associated with this process. Information can also be found on the HRA website: [Update to 'amendment' terminology - Health Research Authority](#) (Cited 11 March 2026)

**Minor Modifications:** Instructions for submitting minor modifications will be as per the modification tool and standard CWOW submission guidance.

**Urgent Safety Measures:** There must be arrangements for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects. In many studies, the individual best able to take these measures will be the Chief Investigator or another identified person or organisation – rather than the Sponsor directly. The protocol should identify the specific individual(s) who accept(s) this responsibility. Otherwise, the Sponsor remains directly responsible. These safety measures, such as temporarily halting the trial (please see below), may be taken without prior authorisation from the MHRA but must be reported to the MHRA, Ethics Committee and sponsor. For all other substantial modifications, MHRA authorisation must be sought before the modification is implemented. For studies that have been processed via the Combined Ways of Working (CWOW) IRAS system, notification of USMs can be done via IRAS rather than email to the MHRA. Selecting project information in as a substantial modification will give the option to indicate if a modification relates to an USM.

### 3.3. Temporarily suspending a trial

A temporary halt of a trial is a stoppage of the trial which is not envisaged in the approved protocol and where there is an intention to resume it. This can be halt of the trial as a whole, of part of a trial, or a stoppage at one or more trial locations to protect participant safety or avoid potential harm to participants (please see the following link for examples of where a temporary halt is not required: [Clinical trials for medicines: collection, verification, & reporting of safety events - GOV.UK](#) (cited 11 March 2026).

To temporarily suspend a trial or part of a trial, submit an application to approve a Route A substantial modification, clearly explaining what aspects of the trial have been stopped and the reason for the suspension. This should be done within 15 calendar days of the trial being temporarily halted.

A temporary halt can be part of an urgent safety measure (USM). In this case, the notification of the temporary halt of a trial should be done via the usual process and following the usual timelines for reporting USMs (please refer to RGIT\_SOP\_037). Failure to notify the licensing authority of the implementation of a temporary halt for safety reasons may be considered a serious breach.

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During the temporary halt, participants should be monitored or followed up. While the trial is halted, the issues of concern should be assessed and revisions to be made to the clinical trial protocol may be required. After this analysis is completed, and reassurance that any potential problem may be solved or mitigated, the sponsor could either restart or end the CT.

To restart a trial after a temporary halt, submit a second application to approve a substantial modification. This application should include evidence that it is safe to restart the trial, including conclusions of the analysis, the mitigation measures if applicable and an updated benefit/risk assessment.

No fixed limit applies to how long a trial can be suspended for, however, the licensing authority and ethics committee will take the suspension duration into account when assessing the application to restart the trial. If the trial is not restarted, guidance on declaring the end of a clinical trial should be followed.

**3.4. 3.3 Submission of non-CTIMP modifications**

Once the Modification tool is Sponsor approved via RGIT and finalised, the modification should be submitted via the online submission process in IRAS and in line with the information contained in the tool's submission guidance tab.

The tool will have generated the overall amendment type and category will be shown in Section 4 of the tool and the submission guidance tab will indicate how the modification should be submitted and to whom.

This guidance must be followed to ensure that the modification is submitted correctly and can be validated. The online modification submission functionality requires a separate login to the researchers main IRAS account.

A new account may need to be set up, the Technical Helpdesk can provide support for this. Once logged in, researchers can refer to the on-screen step-by-step instructions. The system will ask for the IRAS ID to be entered, along with some simple questions about the modification. All the documentation relating to the modification will need to be uploaded and submitted. An automated email will be received to confirm submission of the modification. Upon submission the modification will be shared with REC and/or HRA as applicable.

As noted in section 2.3 above, the HRA has begun rolling out a new digital service, Plan and manage health and care research, which has begun with single-nation, non-NHS REC studies and will expand over time. This service is intended to eventually replace the traditional CWOW/IRAS/Modification Tool submission process. For a study that comes under this category, please contact [RGIT@imperial.ac.uk](mailto:RGIT@imperial.ac.uk) for the relevant resources if needed.

## 3.5. 3.4 Other Submission requirements

### MHRA Device Studies

MHRA Devices must be notified of **all** proposed changes to the investigation (not just those classed as substantial modifications for the purposes of ethical review) and the researcher Chief Investigator must wait for a letter of no objection from MHRA Devices before any changes are implemented.

Any changes to the below are required to be notified to the MHRA:

- the device under investigation
- study documentation, including the clinical investigation plan
- investigators or investigating institutions
- changes requested by an ethics committee

Failure to provide this notification could result in the manufacturer being liable to prosecution.

When notifying the MHRA of any changes, the following information should be provided in writing:

- covering letter with:
- the MHRA reference number for the clinical investigation
- a table with a summary of each proposed change with the reason for each change

Red lined (showing changes being made) and clean copies of all amended study documentation 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 details of who to invoice (full company name, address and registered tax/VAT number).

Notifications should be sent directly to MHRA devices by using the following email address [CI-amendments@mhra.gov.uk](mailto:CI-amendments@mhra.gov.uk). If the files are too big, contact using the same email address to request a link for uploading the documents. Only amendments submitted to this mailbox will be processed.

A fee for amendments to clinical investigations is payable, see [Current MHRA fees - GOV.UK \(www.gov.uk\)](https://www.gov.uk) (cited 12 March 2026). A proof of payment is not required to be attached to applications. Once the amendment application has been validated, an invoice will be sent to make payment for the correct amount.

For further details, please see: [Guidance Notify MHRA about a clinical investigation for a medical device](#)

### Notifying modifications to ARSAC

ARSAC should be notified of any changes concerning the administration of radioactive substances as this may affect the approval granted. Such changes include, but are not limited to:

- Changes to the number of administrations of radioactive substances from Section A1 of the original Preliminary Research Assessment (PRA) form

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- Addition or removal of a procedure involving the administration of a radioactive substance
- Addition of a new study population with a different clinical condition (including changing the age of the participants)
- Addition of healthy volunteers receiving administrations of radioactive substances
- Changes to the radiation risk information in the participant information sheet (PIS) following changes to the protocol addition of healthy volunteers receiving administrations of radioactive substances

Such changes will normally meet the criteria for notifying substantial modifications to the Research Ethics Committee (or GTAC). If you are not sure if your amendment requires ARSAC approval you can contact the Support Unit for guidance by email or telephone prior to submitting your application.

Notification should be made to the ARSAC Support Unit by the sponsor, by email with the following information:

- Short summary of the changes
- Notice of Substantial modification when this is submitted to the REC
- Updated PRA form if there are changes to the number of administrations or procedures involving radioactive substances (note you will need to revise the integrated dataset Part A and/or Part B3 and then create an up to date PDF of the PRA form via the Submission tab)
- Any other relevant enclosures, for example Participant Information Sheet

All information should be emailed to the [ARSAC Support Unit](#).

Once the modification is submitted, ARSAC will send a reference number and details on how and when to pay the £250 fee.

While ARSAC assesses the modification, the researcher remains authorised within the limits of the initial submission and administrations may continue in line with the original application.

Once approval has been granted, individual installations can proceed with the amended study for all procedures on their licence. It is not necessary for each installation to notify ARSAC of modification.

Further guidance may be found on the [ARSAC website](#) or by contacting the [ARSAC Support Unit](#).

## 4. APPROVAL OF MODIFICATIONS

Substantial modifications for CTIMPs and non-CTIMPs require approval from the HRA, favourable opinion from the REC and/or acknowledgement from the MHRA **before** they can be implemented. The only exception to this is where urgent safety measures need to be taken.

If your study is taking place on Imperial College Healthcare NHS Trust premises, or involves Imperial College Healthcare NHS Trust participants, then you must follow the process set out in RGIT\_SOP\_032 to obtain Trust Confirmation of Capacity and

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Capability (CCC) for your study where necessary, **prior** to the modification being implemented. The submission tab in the modification tool will provide guidance on when REC/HRA/MHRA/R&D approvals for the modification are needed.

For ICHT the relevant Divisional Research Manager (DRM) will assess the modification and any supporting documentation for any implications (e.g. regarding funding, contracts or imaging). For studies sponsored by Imperial College London or Imperial College Healthcare NHS Trust and taking place at ICHT, the RGIT will forward a copy of all modification documents and approvals to the ICHT feasibility inbox to facilitate continued running of your study at the Trust. For all external sites, please follow the guidance in the submissions tab regarding provision of documents and approvals to sites.

If the modification tool indicates that your modification is a Category C non-notifiable modification, which does not require REC/HRA/MHRA or R&D approval, sites still need to be made aware of the modification and should be provided with the modification documents and approvals. For ICHT, RGIT will forward these to the ICHT feasibility inbox.

### Transitional Arrangements

The applicable regulations are determined by the date on which the application to approve the substantial modification was submitted, not by whether the trial to be modified is an old rules or a new rules trial. This means that:

- If the sponsor submits an application to approve a substantial modification (or receives notice of a proposed modification by the licensing authority or ethics committee) prior to 28 April 2026, the old regulations apply to the whole process of requesting approval (even after 28 April 2026, if the authorities have not issued a decision by then)
- If an application to approve a substantial modification is submitted on or after 28 April 2026, the amended Clinical Trials Regulations apply to the approval process (even if the clinical trial approval to be modified is for an old rules clinical trial)

Area	Old rules clinical trials (application for clinical trial approval submitted before 28 April 2026)	New rules clinical trials (application for clinical trial approval submitted on or after 28 April 2026)
Applying to modify a clinical trial approval	The Medicines for Human Use (Clinical Trials) Regulations 2004 as in force immediately before 28 April 2026	The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025

## 5. REFERENCES

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

[Update to 'amendment' terminology - Health Research Authority](#)

[IRAS - Amendments for Projects conducted in the NHS/HSC](#)

[IRAS - Maintaining your approvals - Amendments](#)

ICHT Approval of Modifications RGIT\_SOP\_032  
[RGIT SOP 037 Deviations Violations USM v7.pdf](#)

## 6. APPENDICES

None