GOV•UK

Guidance

Clinical trials for medicines: modifying a clinical trial approval

Guidance on the various types of modifications that can be made to a clinical trial approval.

From: **Medicines and Healthcare products Regulatory Agency (/government/organisations/medicines-and-healthcare-products-regulatory-agency)**

Published 25 June 2025

Last updated 8 June 2026 —

Contents

The amended Clinical Trials Regulations took full effect on 28 April 2026. As such, this guidance should now be considered effective and is no longer in draft.

Legal status of this guidance

The following guidance accompanies the Medicines for Human Use (Clinical Trials) Regulations 2004 (https://www.legislation.gov.uk/uksi/2004/1031/contents) ('the Clinical Trials Regulations'), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (https://www.legislation.gov.uk/uksi/2025/538). For assistance in determining whether a clinical trial is within the scope of these Regulations, see the Is it a clinical trial of a medicinal product? (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949145/Algorithm_Clean__1_.pdf) algorithm.

Part 2 of Schedule 1 to the Clinical Trials Regulations requires that the investigator and sponsor (https://www.hra.nhs.uk/planning-and-improving-research/research-planning/roles-and-responsibilities/) (and any individual or organisation that the sponsor delegates trial-related activities to) have regard to all relevant guidance with respect to commencing and conducting a clinical trial. Investigators and sponsors must, therefore, ensure that they are fully aware of the information within this guidance and act accordingly to achieve and maintain regulatory compliance.

Types of modification

Definitions

Per regulation 20 of the Clinical Trials Regulations, a clinical trial approval may be modified by the trial's sponsor, the licensing authority, or the ethics committee.

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

1) Substantial modifications can be 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 the examples section of this guidance

Approval to make substantial modifications must be received from the licensing authority and ethics committee before implementation. The exception to this is for substantial modifications that relate to urgent safety measures

(https://www.gov.uk/guidance/clinical-trials-for-medicines-collection-verification-reporting-of-safety-events#urgent-safety-measures-usms). When considering implementing substantial modifications, sponsors should assess whether such modifications alter the original clinical trial approval to the extent that it should be considered a new clinical trial. If this is the case, a new application for clinical trial approval should be submitted.

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 (https://www.gov.uk/guidance/clinical-trials-for-medicines-modifying-a-clinical-trial-approval#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 (however, other approvals may be required, 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.

Determining modification type

It is the sponsor's responsibility to assess, using a risk-based approach, whether a modification is substantial, minor or a modification of an important detail.

For modifications deemed substantial, the sponsor is then responsible for determining whether it is a Route A substantial modification or a Route B substantial modification. If the change meets the definition of a Route B substantial modification, it is eligible for automatic approval by the licensing authority (https://www.gov.uk/guidance/clinical-trials-for-medicines-modifying-a-clinical-trial-approval#automatic-approval-of-route-b-substantial-modifications-by-the-licensing-authority). The justification for this decision should be clearly documented. In determining whether a substantial modification is Route A or Route B, note that a modification is considered a Route B substantial modification (and therefore is eligible for automatic approval from the licensing authority) based solely on the nature of the modification itself and is independent of whether the clinical trial was authorised via automatic authorisation (https://www.gov.uk/guidance/clinical-trials-for-medicines-notifiable-trials).

For further support in determining the correct category for a modification, review the decision tree for determining the correct category for a modification (https://assets.publishing.service.gov.uk/media/6a26b34d56e988a798b38796/Fig1._Modification_types.pdf) and the tables in the following section. Note that in most cases it is possible to include multiple modifications of different categories in a single application to the authorities. The exception to this is that certain modifications of an

important detail cannot be submitted at the same time as any other modification. See the Step-by-step guide to using IRAS for combined review (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-review/step-step-guide-using-iras-combined-ways-working-cwow/#amendment) for more details. The sponsor must select the route of submission according to the modification in the application that requires the highest level of scrutiny by the authorities (e.g. if the application includes any Route A substantial modifications, the whole application must be submitted through the Route A substantial modification process).

Examples of modifications

Route B substantial modifications

The table below includes all modifications that are currently considered to be Route B substantial modifications.

Note that for a modification to be considered a Route B substantial modification, the sponsor, having made reasonable enquiries, must not be aware of any new significant safety concerns with the investigational medicinal product(s) (IMPs) that have arisen since the clinical trial was approved. If the sponsor is aware of new significant safety concerns, the modification is not a Route B substantial modification, even if it otherwise meets the criteria below.

Tab1. Route B substantial modifications in Modifying a Clinical Trial Approval (https://assets.publishing.service.gov.uk/media/69e6413059ffffb9ecfcf964/Tab1._Route_B_substantial_modifications_in_Modifying_a_Clinical_Trial_Approval.pdf) (PDF, 192 KB, 2 pages)

Note that where a Route B substantial modification 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.

Modifications of an important detail

The information below includes all modifications that are currently considered to be modifications of an important detail.

- Changes to the trial identification
- Change in duration of the trial, provided that that none of the following apply:

  - there is a change in how the end of trial is defined,
  - exposure to treatment is extended, or
  - there is a change to monitoring arrangements
- Changes in the contact details of the sponsor, sponsor's legal representative or chief investigator
- Change to the principal investigator at a non-NHS/HSC trial location in a multi-centre trial
- Addition of new trial locations not listed with the original request for approval, where there are no additional documents for submission
- Changes to the sponsor or the sponsor's legal representative
- Changes to a protocol approved under the regulations in place before 28 April 2026 that are only to provide alignment with the new requirements under the Clinical Trials Regulations, including technical or organisational measures
- Date of recruitment of the UK first participant

Route A substantial modifications and minor modifications

The table below provides examples of Route A substantial modifications and minor modifications but should not be seen as an exhaustive list.

Changes to the protocol

	Route A substantial modification	Minor modification
Changes to primary or secondary endpoints that have a significant impact on the safety or scientific value of the clinical trial	×	
Changes to exploratory or tertiary endpoints		×
Changes to IMP(s) (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)	×	
Change to the dosing of IMP(s), including dose level, regimen, route of administration and formulation	×	

New toxicological or pharmacological data relating to the IMP(s) (including new interpretations of data) that impacts on the risk and benefit assessment	×	
Addition of a trial arm or placebo group	×	
Changes in the number of participants per trial location, if any change is insignificant in view of the absolute number of participants		×
Significant change in the absolute number of trial participants	×	
Changes to diagnostic or medical monitoring procedures that have a significant impact on the safety or scientific value of the clinical trial	×	
Change to the number of participant safety monitoring visits for a phase I or II trial	×	
Changes to the assessments that form the participant safety monitoring visits	×	
Changes in the processes associated with recording keeping used by the research team for recording trial data		×
Withdrawal of an independent Data Safety Monitoring Committee	×	
Removal or re-wording of any contraceptive requirements	×	
Change to stopping rules for any part of the trial (individual, cohort, dose escalation, whole trial, etc.)	×	
Change to or addition of exemptions to the recording of serious adverse events (SAEs)	×	
Changes due to acute issues with participant safety that have already been implemented via USM	×	
Protocol clarification letters		×

Changes to the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)

	Route A substantial modification	Minor modification
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	×	
The addition of new expected events to the reference safety information (RSI) or where life-threatening or fatal events are now expected, where this changes the initial risk and benefit assessment of the study or the safety profile of the IMP that was approved by the authorities	×	
Changes to the reference safety information (RSI) involving a decrease in frequencies	×	
Changes to the format of the RSI, provided there is no change to the content		×
IB erratum		×

Other modifications

	Route A substantial modification	Minor modification
Notification of a temporary halt to all or part of a trial	×	
Request to restart a trial following a prior temporary halt (even if no protocol update is required)	×	
Resubmission of a prior modification that was not approved (except for rejection due to failed validation only)	×	
All or part of the modification is in response to a previous condition of approval from the licensing authority	×	

Internal changes to the sponsor's organisation		×
Revocation, suspension or significant changes (such as implementation of safety changes) of the IMP's marketing authorisation in any region	×	
Revocation, suspension or significant changes (such as implementation of safety changes) of the non-investigational medicinal product's (NIMP) marketing authorisation in any region	×	
Any global changes associated with the use of the IMP, such as significant safety concerns raised by another regulator, trials using the IMP halted	×	
Changes in the logistical arrangements for storing or transporting samples		×
Changes in technical equipment		×
Addition or deletion per se of a third country		×

Applying for approval of a substantial modification

Submitting an application for approval of a substantial modification

To request approval for a Route A or Route B substantial modification to a clinical trial approval:

- for trials approved through the combined review process, submit a single application (including all documentation) through the Integrated Research Application System (IRAS). Detailed guidance on using IRAS to submit an application for clinical trial approval can be found on the Health Research Authority (HRA) website (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#making)
- if the clinical trial to be modified was not originally approved through the combined review process, submit applications to both the licensing authority (via MHRA Submissions (https://www.gov.uk/guidance/register-to-make-submissions-to-the-

mhra#gaining-access-to-mhra-submissions)) and the ethics committee (via the online portal on IRAS (https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission))

There are fees applicable to submission of an application to modify a clinical (https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#clinical-trials-application-fees) trial approval. To pay these fees, refer to the guidance on making a payment to MHRA (https://www.gov.uk/guidance/make-a-payment-to-mhra).

For some types of substantial modification, submitting multiple applications for approval in parallel may be possible. Refer to the HRA website (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#amendment) for further guidance.

Validation of applications

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 (and through IRAS, for trials approved through combined review) within 7 calendar days of submission.As soon as possible during this 7-day period, and no later than on the fifth calendar day, 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 this 7 days, the application will be invalidated and the applicant will need to resubmit the application with the deficiencies corrected.

Before preparing an application, review the common reasons for an application to be found invalid (https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications/common-issues-validation) by the licensing authority.

Initial review of applications by the authorities

For Route B substantial modifications, see the guidance on Automatic approval of Route B substantial modifications by the licensing authority.

Valid applications for Route A substantial modifications 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

In exceptional circumstances, the licensing authority or ethics committee may need to consult with a relevant committee or specialist group (https://www.gov.uk/guidance/clinical-trials-for-medicines-expert-advice) before issuing a decision on an application for a substantial modification.

Approval with conditions

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 implementation must be reversed.

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

Requests for further information

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. 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 (to the licensing authority through

MHRA Submissions and by email to the relevant ethics committee), 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 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 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 (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).

The full process is summarised in the figure below. Note that this diagram shows the maximum possible timelines (including sponsor-driven timelines). The time to a decision will be shorter than this for almost all applications.

Flowchart summarising the process of applying for approval of a Route A substantial modification (https://assets.publishing.service.gov.uk/media/6954088ae8f9a8d94d8d18c1/Figure_2._Flowchart_summarising_the_process_of_applying_for_approval_of_a_Route_A_substantial_modification.pdf).

Automatic approval of Route B substantial modifications by the licensing authority

Identifying Route B substantial modifications

To enable a streamlined, risk-proportionate approach to its review of applications, the licensing authority is designating some substantial modifications as Route B substantial modifications. Applications to approve these modifications will receive automatic approval from the licensing authority. As the ethics committee processes Route B substantial modifications in the same way as Route A substantial modifications, if a Route B substantial modification requires review by the ethics committee as well as the licensing authority then the initial combined decision on approval of the Route B substantial modification will be issued within 35 calendar days of validation.

If the applicant identifies that a modification is a Route B substantial modification,

per the criteria in regulation 11B of the Clinical Trials Regulations and as clarified in Route B substantial modifications, they must indicate this in the cover letter accompanying the submission.

Where an application is for a Route B substantial modification but is incorrectly submitted as a Route A substantial modification, the application may be invalidated and will need to be resubmitted correctly.

The licensing authority will monitor and may audit use of this scheme.

Note that if a single application to make a substantial modification includes multiple changes, all changes must qualify as Route B substantial modifications in order for the application to be eligible for automatic approval from the licensing authority.

Submission process

Submit applications for approval of Route B substantial modifications through the same process as for a Route A substantial modification with the same accompanying documents. In addition to the standard accompanying documents, the applicant must complete the Confirmation of Route B substantial modification criteria form (https://assets.publishing.service.gov.uk/media/69e6439e84ac36aaf2cc9309/Confirmation_of_Route_B_Substantial_Modification_Criteria_V1.0.docx) and submit this with their application. The cover letter must also include a statement that the application is for approval of a Route B substantial modification.

The same documents should be submitted because:

- this documentation may be required for the ethics committee review, which follows the same process for both Route B substantial modifications and Route A substantial modifications
- if the licensing authority does not provide automatic approval and instead conducts a full review of the application, all necessary documentation will have already been provided
- the documentation may be needed to facilitate any audit or inspection of applications for approval of Route B substantial modifications that the licensing authority wishes to undertake

Additional information should be also submitted as part of the full application per the table below.

Route B substantial modification	Additional information
All changes to a non-first-in-human trial have been reviewed and	Confirm in the submission the regulatory authority that has approved the modification

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	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.

Outcome
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:

- 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.

The full process is summarised in the figure below. Note that this diagram shows the maximum possible timelines, so the time to a decision may be shorter than this.

Flowchart summarising the process of applying to the licensing authority for automatic approval of Route B substantial modifications (https://assets.publishing.service.gov.uk/media/68dbc85949e17d00a56ffc12/Fig3._Route_B_substantial_modification_applications.pdf).

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 of their intention to appeal the licensing authority decision. Per Schedule 5 of the Clinical Trial Regulations, the licensing authority will then inform the Commission on Human Medicines (CHM), and CHM will give the applicant a period of 6 months in which to provide:

- either written representations concerning the decision or a written summary of the oral representations that they intend to make
- any supporting documents

CHM may agree an extension to this 6-month period if requested by the applicant, up to a maximum of 12 months.

If the applicant has chosen to make oral representations to CHM, this will be arranged following receipt of the written summary and supporting documents.

After reviewing the applicant's representations, CHM will report its findings and advice to the licensing authority. The licensing authority will consider CHM's report and either confirm or change its decision regarding the application for approval of a substantial modification.

If the applicant remains dissatisfied with this decision, they may notify the licensing authority at appeals@hra.nhs.uk that they wish to appear before or be heard by a person appointed by the licensing authority, and will then a period of 3 months in which to provide:

- a written summary of the oral representations that they intend to make
- any supporting documents

- confirmation of whether they wish the hearing to be public

Following the hearing, the appointed person will provide a report to the licensing authority. The licensing authority will then make a final decision regarding the application for approval of a substantial modification.

For guidance on the process for appealing a decision by the ethics committee, refer to the guidance on the HRA website (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/clinical-trial-regulations-reform/guidance-on-changes-to-the-clinical-trials-regulations/the-approvals-process-for-clinical-trials/the-approvals-process-for-modifications-amendments/).

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 (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#withdrawing)
- for applications made separately to the licensing authority and ethics committee, contact MHRA at 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.

Documents that should accompany an application to make a substantial modification

Cover letter

The cover letter should include the following:

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

Modification tool

The modification tool is a resource available on IRAS (https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool) (or by contacting the licensing authority at clintrialhelpline@mhra.gov.uk, for trials not approved through combined review) to assist in determining whether the application needs to be reviewed by the licensing authority, the ethics committee, or both (although the application must be submitted to both authorities in all cases). Once completed, the output of the modification tool should be included in the application for approval of a substantial modification.

If the same substantial modification impacts many non-combined review trials, the sponsor can make a single application through MHRA Submissions covering all relevant trials (in addition to the application to the ethics committee through IRAS). In this case, the sponsor should complete and submit the Substantial modification notification form (https://assets.publishing.service.gov.uk/media/69a71499a2495f2d259f13f6/Substantial_modi

fication_notification_form.docx) (MS Word Document, 16 KB) instead of the modification tool. Note that bulk submission of modifications is not currently possible where any of the trials affected were approved through the combined review process.

Other documents

Depending on the nature of the modification, the applicant may also need to submit the following:

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

This guidance does not include documents are reviewed only by the ethics committee. These documents, and optional documents that may be submitted alongside the application for approval of a substantial modification can be found on the HRA website (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/document-management-combined-review-applications/).

Notifying the authorities about a modification of an important detail

If the sponsor makes a modification of an important detail, they must subsequently notify the authorities of this change. Instructions for notifying the authorities about a modification of an important detail are provided on completion of the modification tool (https://www.gov.uk/guidance/clinical-trials-for-medicines-modifying-a-clinical-trial-approval#modification-tool). No fees are associated with this process.

Note that all sponsors will need to notify the authorities of the date on which the first UK participant was recruited to a clinical trial through the modification of an important detail process, in order to demonstrate that the trial has been registered in a public registry within the applicable deadline and to support the licensing authority in monitoring the trial's approval status (https://www.gov.uk/guidance/clinical-trials-for-medicines-ending-a-clinical-trial#lapse-of-clinical-trial-approval).

Modifications by the licensing authority or ethics committee

Under regulation 21(1) of the Clinical Trials Regulations, either or both of the licensing authority or ethics committee ('the appropriate authority') may require the sponsor to make modifications to a clinical trial to ensure the trial's safety or scientific validity or to ensure adherence to the principles of good clinical practice.

Sponsors will receive a notification of the proposed modification, and the reasoning behind the proposal, via email at least 7 calendar days before the modification is set to take effect. The sponsor may accept the proposal, or otherwise has 7 calendar days to submit representations against the proposal in writing to the relevant authority.

The appropriate authority will issue a final decision on whether the modification must be implemented after considering the sponsor's representations. The date on which the proposed modification is to take effect may be delayed so that the appropriate authority has sufficient time to consider these.

If the proposed modification is implemented, if it meets the definition of a substantial modification then the sponsor must submit an application for approval of a substantial modification. The licensing authority will provide guidance on how and when this application should be submitted.

Where the appropriate authority makes a final decision to modify a clinical trial approval, the sponsor has 28 calendar days from the date on which the decision letter was issued to provide written notice to the authorities of their intention to appeal. This notice should be sent to appeals@hra.nhs.uk, after which the authorities will contact the applicant to discuss the appeals process. Where the decision to modify the clinical trial has been made by the ethics committee, the notice must also set out the sponsor's representations (and this is also encouraged where the decision to modify the clinical trial has been made by the licensing

authority).

Published 25 June 2025
Last updated 8 June 2026 + show all updates