



Modifications SOP

Document control use only	
Reference	R&D SOP 08
Directorate / Care Group	Research & Development
Version	Version 6
Result of last review	Regulatory Changes
Issue date	23/04/2026

Author / Owner Use Only	
Group or Trust specific document	HHP (Group) – Hull University Teaching Hospitals NHS Trust, Northern Lincolnshire and Goole NHS Foundation Trust
Date approved by owner (for minor changes only outside committee)	N/A
Date approved	13/5/2026
Approving body	R&D Sponsor Oversight Group / RDI Committee
Next full review date	12/05/2029
Lead Director	Professor Sathyapalan – R&D Director James Illingworth – R&D Manager
Document type	Standard Operating Procedure
Author / Contact	Leanne Cox – R&D QA Manager
Key words	GCP, SOPs, R&D, Research & Development

Distribution:	HHP R&D internet Click on GCP SOPs for HHP-sponsored CTIMPs https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/
When this document is viewed as a paper copy, the reader is responsible for checking that it is the most recent version. Printed copies valid only if separately controlled	
© Humber Health Partnership 2026 All Rights Reserved No part of this document may be reproduced, stored in a retrieval system or transmitted in any form or by any mean without the prior permission of Humber Health Partnership R&D department.	
AI update statement: This Standard Operating Procedure (SOP) was reviewed and updated with the assistance of an Artificial Intelligence (AI) tool. The AI output was used to support drafting and editing only; all content was verified, amended where required, and approved by the document owner/author in accordance with the Trust's document control and governance requirements.	

Authorized by	Sign	Date
R&D Director	Professor Thozhukat Sathyapalan	13/5/2026
R&D Manager	James Illingworth	13/5/2026

This page details the version history and the main changes **made for each new** version.

Version Log		
Version number and date	Author	Details of significant changes
Version 1, 04.03.11	J Pacynko	Original SOP approved by R&D Committee on 04.03.11 by global email. R&D Committee reviewed SOP on 24.02.11, but meeting not quorate.
Version 2, 10.08.11	J Pacynko	<ul style="list-style-type: none"> - To emphasize that investigators are required to submit substantial Modifications proactively and <u>in a timely fashion</u> to MHRA and/or Ethics. - Up-date HHR&D internet links for GCP SOPs & docs. - HHR&D GCP SOPs are defaulted to for hosted trials with no SOPs.
Version 3, 12.11.14	J Pacynko	<ul style="list-style-type: none"> - Internet links up-dated - Creation and submission of the substantial Modification form via IRAS - Minor changes to methods of submission to MHRA, REC and R&D. - Filing all correspondence regarding Modifications in the TMF. - 'Extension of the study beyond the period specified in the application form' has been added to non-SA list in Appendix 2.
Version 4, 04.02.19	J Pacynko	<ul style="list-style-type: none"> - Further detail added on substantiality decision process and documenting the decision. -Added that for single-site trials the R&D monitor will prepare and submit Modifications. For multi-site trials, managed by a CTU, the CTU trial co-ordinator will prepare and submit Modifications. -Working instructions 11a and 11b contain more detailed instructions on how to prepare and submit substantial and non-substantial Modifications and must also be used by R&D QA/CTU trial co-ordinator to green-light Modifications. -Methods of submission to REC, HRA and MHRA up-dated. -Confirmation of capacity and capability to incorporate Modification changes is now issued by R&D instead of R&D approval. -If one or more sites of a multi-site trial are temporarily halted, this has to be notified to the MHRA, REC and HRA by submission of a substantial Modification.
Version 5, 09.11.21	S Moffat	<ul style="list-style-type: none"> - Change of CESP details to MHRA Submissions Portal - Change of IRAS details for submitting Modifications - Addition of Appendix 5 – email templates

Version 6,	G Constable	Updated in line with IRAS’s Combined Review process. Correcting department name from Research and Development (R&D) to Research, Development and Innovation (RDI).
Version 7, 20.01.2026	L Cox	Aligned with ICH E6 (R3); introduced risk-proportionate modification assessment, critical-to-quality focus, clarified Sponsor Oversight and fit-for-purpose documentation Title of SOP has changed in line with the new ‘Modifications’ instead of Amendments. Update from HUTH to HPP incorporating both HUTH and NLaG.

Section no.	Contents	Page no.
1	Introduction	4
2	Purpose	4
3	Who should use this SOP	5
4	Sponsor’s decision	5
5	Who prepares and submits modifications	5
6	Minor Modifications	6
7	Modifications of an important detail	7
8	Substantial modifications <ul style="list-style-type: none"> • Definition • Preparation and submission • Green-light and implementation 	7 7 9
9	Documenting in the Trial Master File (TMF)	9
10	Implementation	9
Appendix 1	Modification timeframe and process	10
Appendix 2	Notification of substantial modifications to CTIMPs <ul style="list-style-type: none"> • Route A Submission 	11

	<ul style="list-style-type: none"> • Route B submission • MHRA Modification Decision Tree • Apply to change your trial’s protocol or documentation 	
Appendix 3	Examples of modifications of an important detail of minor modifications	13
Appendix 4	Examples of Minor Modifications	14
Appendix 5	Email templates used to notify participating NHS organisations in England and Wales of an Modification.	14

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the R&D GCP SOPs are available at:

<https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/>

1 Introduction

- 1.1 This SOP applies to clinical trials of investigational medicinal products (CTIMPs) sponsored by **Humber Health Partnership**.
- 1.2 During the course of a trial, it may be necessary to make changes to the trial protocol or other trial documents, **trial processes, systems, or oversight arrangements**.
- 1.3 **Modifications** are changes made to a clinical trial after REC favourable opinion, MHRA clinical trial authorisation and HRA approval has been obtained.
- 1.4 A modification can be **substantial, modifications of an important detail, and minor modifications**.
- 1.5 It is the Sponsor’s legal responsibility to decide whether a **modification** is substantial, **a modification of an important detail** or **a minor modification** and which approvals are required. It is the Chief/Principal Investigator’s responsibility to submit substantial **modifications** proactively and in a timely fashion.
- 1.6 **Modifications must be assessed using a risk-proportionate approach, focussing on whether the change has a meaningful impact on participant safety, rights and wellbeing, or the reliability of trial results (critical-to-quality factors)**.
- 1.7 **The legal requirements for modifications made by the Sponsor are set out in Regulations 24 and 25 of the Medicines for Human Use (Clinical Trials) Regulations 2004 and associated UK guidance.**
- 1.8 **This SOP is aligned with ICH E6 (R3) Good Clinical Practice, which replaces earlier guidance by embedding quality-by-design, proportionate risk management, and fit-for-purpose documentation throughout the trial lifecycle.**

2 Purpose

- 2.1 The purpose of this SOP is to describe the procedures and responsibilities for notifying, obtaining approvals and implementing **Modifications** to HUTH-sponsored CTIMPs.
- 2.2 **This SOP ensures that modifications are managed in a manner that is proportionate to their potential impact on critical trial factors.**
- 2.3 This SOP also describes the procedure for submitting substantial **modifications** for the temporary halt and restart of a trial and the procedure for early termination **where applicable.**

3 Who should use this SOP

- 3.1 **This SOP applies to all research, pharmacy, CTU and R&D staff involved in HHP sponsored CTIMPs, including those with delegated trial oversight, quality, data, or system responsibilities.** Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no relevant SOP, **HHP RDI SOPs** are defaulted to in this case.

4 Sponsor's decision

- 4.1 The legal and overall responsibility to decide whether a **Modification** is substantial lies with the Sponsor. The MHRA call this the 'substantiality decision'.
- 4.2 **The substantiality decision must be informed by an assessment of risk and impact on critical-to-quality factors rather than solely by volume or number of documents affected.**
- 4.3 The RDI QA team, acting as Sponsor representatives, require the CI/PI to notify them of any planned changes or emerging changes to the trial.
- 4.4 RDI QA will decide whether a **modification** is substantial, **a modification of an important detail or non-substantial and which regulatory bodies must be notified. Advice may be sought from the CI/PI, REC or MHRA where appropriate.**
- 4.5 **The assessment and rationale for the substantiality decision must be documented, demonstrating consideration of participant safety, data integrity, trial conduct, and system reliability.**
- 4.6 **For any modification that may affect participants' willingness to continue, Sponsor must assess need for updated PIS/ICF and re-consent, obtain REC/IRB approval prior to use, and document decision + communication to participants/sites.**
- 4.7 The substantiality decision will be documented on the Study Tracking/**Modifications** Log.

5 Who prepares and submits **modifications**

- 5.1 For single-site trials, **modifications will be prepared and submitted by the RDI monitor in collaboration with the PI.**

- 5.2** For multi-site trials managed by a clinical trials unit (CTU), modifications will be prepared and submitted by the CTU, with Sponsor oversight provided by RDI QA. RDI QA will need to review the documents before authorising modifications. Delegation of modifications preparation or submission does not transfer Sponsor accountability, which remains with HPP.
- 5.3** The Modification Tool applies to all project-based research and should be completed when preparing to submit a modification. Instructions on how to complete the Modification tool and how to submit a modification online can be found on the IRAS website <https://www.myresearchproject.org.uk/help/hlpModifications.aspx#Modification-Tool>
- 5.4** If a modification changes delegated activities/service provider scope, Sponsor must ensure agreements are updated, oversight arrangements adjusted (KPIs/escalation/communication), and evidence filed in TMF/SSF.

6 Minor Modifications

Definition

- 6.1** 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.
- 6.2** Examples of minor modifications can be found in Appendix 3 using the link.
- 6.3** **Working instruction 11b, the Minor Modifications Green-light Checklist**, must be used by those staff preparing and submitting minor Modifications.
- 6.4** All minor Modifications must be recorded on the Study Tracking or Modifications Log. This log is requested by the MHRA during inspections. The Study Tracking/Modification Log is kept up-to-date by the RDI monitor or by the CTU trial coordinator.
- 6.5** See the MHRA website (link below) on how to inform the MHRA of changes to the contact person for a CTA.
<https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#change-your-contact-details>
- 6.6** The minor Modification can only be implemented when all relevant approvals including RDI C&C have been received. This is the green-light for the Modification to be implemented.
- 6.7** Once the green-light has been issued, the implementation email can be sent to site(s). Please see the links to Modification notification email templates in Appendix 5.
- 6.8** Up until then, the trial can continue on the basis of the original/previously approved documentation.

7 Modifications of an important detail

Definition

- 7.1 Modifications of an important detail do not significantly impact on 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](#)
- 7.2 Examples of Modification of an important detail can be found in Appendix 3 using the link.
- 7.3 No fees are associated with this process.
- 7.4 Note that all sponsors 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, 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](#).
- 7.5 The Modification of an important detail can only be implemented when all relevant approvals including RDI C&C have been received. This is the green-light for the Modification to be implemented.
- 7.6 Once the green-light has been issued, the implementation email can be sent to site(s). Please see the links to Modification notification email templates in Appendix 5.
- 7.7 Up until then, the trial can continue on the basis of the original/previously approved documentation.

8 Substantial modifications

Definition

- 8.1 Substantial modifications are considered to be a modification to a clinical trial approval which is likely to have a substantial impact on the safety or rights of participants or on the reliability or robustness of the data generated by the trial. For modifications to eliminate an immediate hazard, sponsor must document the hazard, action take, cause assessment and submit any protocol changes in modifications.
- 8.2 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.
- 8.3 Examples of substantial modifications and how to categorise are given in Appendix 4.
- 8.4 This definition reflects the ICH E6 (R3) emphasis on critical-to-quality factors rather than administrative classification alone.
- 8.5 RDI QA staff will review the substantial modification documents before authorisation.

Preparation and submission

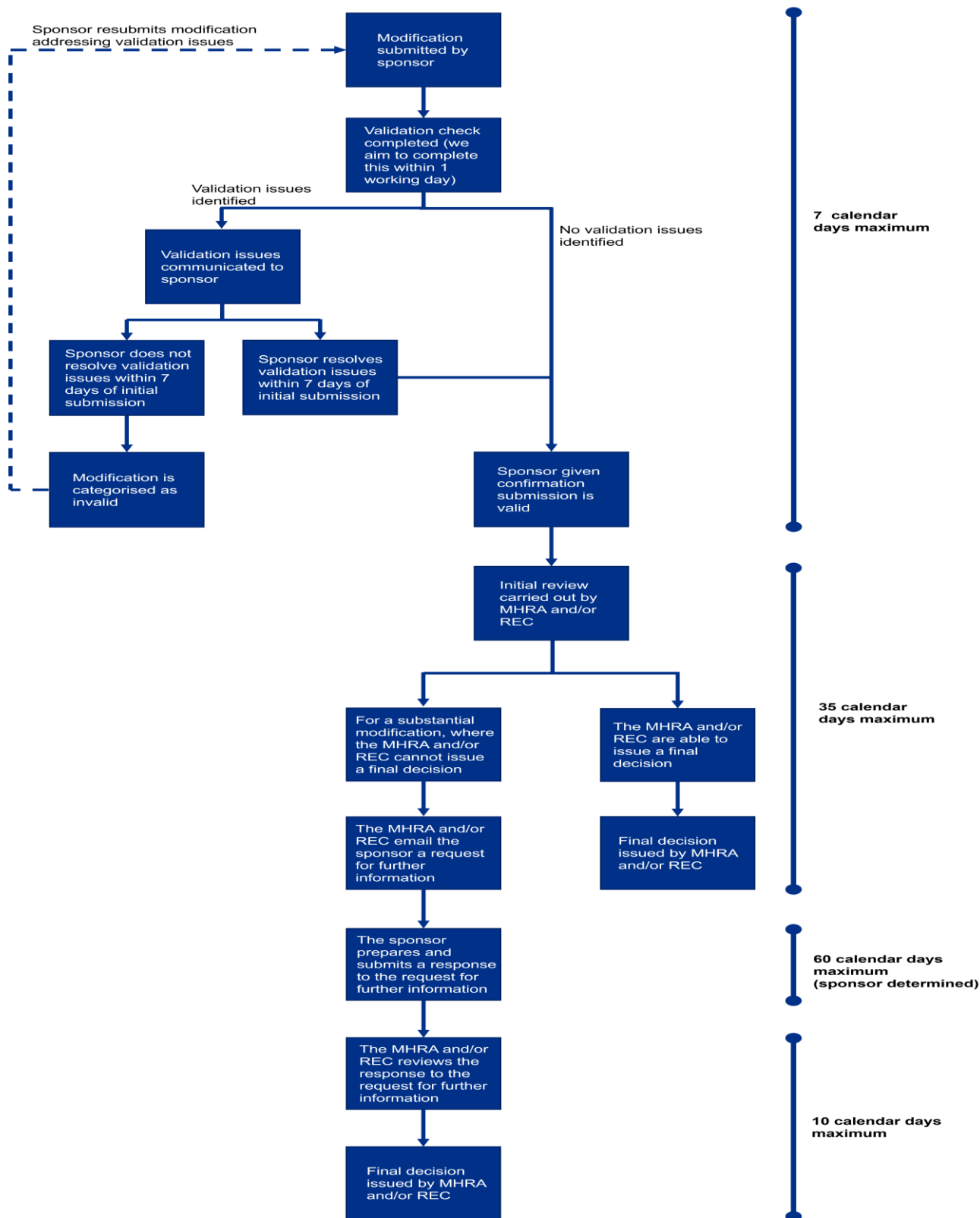
- 8.6** Substantial modifications must be prepared and submitted proactively and in a timely manner.
- 8.7** The scope of the documentation submitted must be proportionate and focused on information relevant to the change and its impact.
- 8.8** For clinical trials authorised via the combined review process the modification should be prepared and submitted using the new part of Integrated Research Application System (IRAS).
 To access this, you must log in to the IRAS Identity Gateway which is a separate log in to your main IRAS account. Guidance can be found on <https://www.myresearchproject.org.uk/help/hlpModifications.aspx#Online-Submission>.
- 8.9** For clinical trials not approved or yet transitioned over to the combined review process, you should continue to use MHRA submissions portal. Guidance can be found by using R&D WI 47 MHRA Submission and also on the MHRA website using the link below: <https://www.gov.uk/guidance/register-to-make-submissions-to-the-mhra>
- 8.10** The completed Modification Tool form should be transferred via IRAS to the RDI Manager to be authorised electronically on behalf of the Sponsor. Instructions are clearly given in IRAS.
- 8.11** The MHRA or REC will check to make sure it's valid and communicate the outcome of the validation check within 1 working day of it being submitted. If the MHRA or REC identify any issues with the modification, the Sponsor will be asked to address these within **7 calendar days** of when they submitted the substantial modification request. If the issues cannot be addressed within 7 days, the MHRA and/or REC will categorise the substantial modification request as invalid. This means the modification will need to be resubmitted, making sure the issues identified in the initial validation process are addressed.
- 8.12** Once a substantial modification request is confirmed as valid, it will be reviewed and an outcome will be issued within **35 calendar days**.
- 8.13** If a request for further information is required, it will be sent within **35 calendar days** of the substantial modification request being confirmed as valid. If a request for further information is received, there is a maximum of **60 calendar days** to respond. A response can be submitted at any point within the 60-day timeframe. Failure to respond within 60 days, then substantial modification request will not be authorised by the MHRA and will be given an unfavorable opinion by the REC. If a longer timeframe is needed to prepare a response to the request for further information, then a request for an extension can be made by emailing the MHRA at clintrialhelpline@mhra.gov.uk
- 8.14** For RDI, send all the modification documents to the RDI lead. RDI will forward a copy of the substantial modification documents to clinical trials pharmacy staff and all other relevant service providers that the modification affects (e.g. labs, radiology etc) to check the departments have the capacity and capability to incorporate the changes. If the departments are in agreement, R&D will provide confirmation of capacity and capability.

Green-light and Implementation

- 8.15** *Working instruction 11a, the Substantial Modification Green-light Checklist, must be used by those staff preparing and submitting substantial Modifications. Sponsor green light for a modification must confirm whether CtQ factors, risk assessment and any QTLs/acceptable ranges require update, and whether the monitoring plan requires update; revised plans must be filed before implementation.*
- 8.16** The modification is not implemented until all required regulatory approvals have been obtained and Sponsor green-light has been issued.
- 8.17** Sponsor green-light confirms that the risks introduced by the modification have been assessed, approved by relevant authorities, and that trial systems, staff and sites are ready to implement the change safely and consistently. If there are computerised systems changes, sponsor must ensure documented change control, risk-based validation & its release after approvals.
- 9 Documenting in the Trial Master File (TMF)**
- 9.1** Documentation relating to modifications must be sufficient to demonstrate compliance, oversight, and decision-making, and include fit-for-purpose documentation. If data capture is affected, Sponsor should assess and document any data governance impacts.
- 9.2** Both paper and electronic TMFs must clearly show what has changed, why it has changed, who approved the change, and when it was implemented. If the record location has been updated then this should be recorded.
- 10 Implementation**
- Implementation of this SOP will conform to the process outlined in [R&D SOP 01 Management of SOPs](#).

Appendix 1

Modification timeframe and process



Appendix 2

Notification of substantial **Modifications** to CTIMPs

It is the legal responsibility of the Sponsor to decide whether a substantial modification requires MHRA authorisation and/or an ethical opinion.

Substantial modification

The changes below are examples of substantial modifications:

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

Examples of Route A

A list of substantial modifications can be found using this link

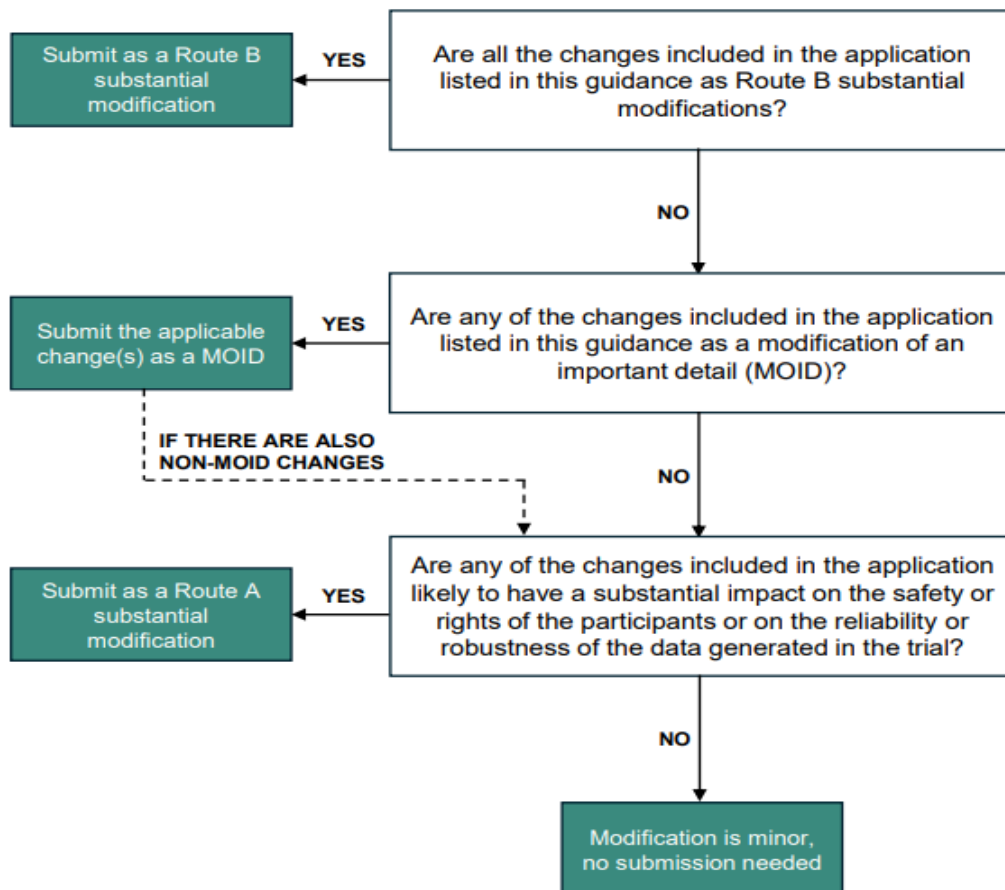
[Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](https://www.gov.uk/guidance/clinical-trials-for-medicines-modifying-a-clinical-trial-approval)

Examples of Route B

A list of Route B can be found using this link

https://assets.publishing.service.gov.uk/media/68dbc859ef1c2f72bc1e4c33/Tab1_Route_B_substantial_modifications.pdf

How to categorize a substantial Modification using the MHRA Decision Tree



Taken from the Gov.uk website: <https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#apply-to-change-your-trials-protocol-or-documentation>

Apply to change your trial’s protocol or documentation

These changes count as a substantial Modification to your clinical trial authorisation. You need to send a notification of Modification form, a revised application form and the following documents to the Medicines and Healthcare products Regulatory Agency (MHRA):

- Covering letter detailing the trial reference numbers (IRAS, CTA number, EudraCT etc) along with Purchase Order Number, outlining the substantial changes (if there have been any non-substantial changes please also outline these separately)
- A pdf copy of the locked [Modification tool](#). You should ensure that the Modification tool contains a clear description of the substantial Modification and reasons for the proposed changes. Alternatively, for ‘bulk’ Modifications (where the same change affects many trials), the substantial Modification notification form** can be completed and submitted. The form is available [here](#).

- PDF file of the [Clinical Trial Authorisation application form](#)* generated in IRAS with changes highlighted, if the Modification affects the information previously submitted.
- Copy of the proposed changes to the protocol or any other documents (e.g. IMPD), showing previous and new wording where applicable supporting data for the Modification, including as applicable:
 - Summaries of data
 - Updated overall risk benefit assessment
 - Possible consequences for subjects already in the trial
 - Possible consequences for the evaluation of results

Appendix 3

Examples of modifications of an important detail

Taken from HRA Website

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

The changes below are examples of modifications of an important detail:

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

Appendix 4

Examples of Minor Modifications

Taken from HRA website

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

The changes below are examples of minor modifications:

- changes in the number of participants per trial site, if any change is insignificant in view of the absolute number of participants
- changes in the processes associated with recording keeping used by the research team for recording trial data
- internal changes to the sponsor's organisation
- changes in the logistical arrangements for storing or transporting samples
- changes in technical equipment
- minor changes to the protocol or other study documentation, for example correcting errors, updating contact points, minor clarifications

Appendix 5

The following template emails can be used to notify participating NHS organisations in England and Wales of an Modification:

- [Template email for sponsors to share category A or B Modification documents with sites \(regulatory approvals outstanding\)](#)
- [Template email for Category A or B Modification documents with sites – where regulatory approvals in place](#)
- [Template email for sponsors to share category C Modification documents with sites](#)
- [Template email for sponsors to confirm implementation of an Modification](#)

DRAFT