Effective management of amendments to research studies: Principles for UK approach

Introduction

This approach for the management of amendments relates to changes made to a research study[1] **after HSC/NHS Research and Development (R&D)** permission (Scotland/Northern Ireland) or HRA and HCRW Approval (England/Wales) is granted.[2] These amendments may be 'substantial' or 'non-substantial', which is determined by the sponsor of the research study. The amendment tool will help sponsors make this decision.

All amendments to a research study are expected to be implemented in a timely manner unless any regulatory authorisation/ approval body does not give their approval or HSC/NHS organisation objects to their implementation.

The management of amendments can represent a significant workload for HSC/NHS R&D offices and researchers. The Health Research Authority (HRA) and Devolved Administrations have agreed to streamline the management of amendments by introducing a system of categorisation of amendments for R&D purposes. This categorisation will ensure that amendments are handled in a manner that is appropriate to the scale of the amendment and the potential risks to, and the liability of the organisation implementing the amendment. The amendment tool provides this information prior to submission for sponsors.

This document outlines the guiding principles that are intended to underpin the approach for managing amendments by HSC/NHS R&D offices across the UK. The attached annexes provide further detail on the operation and delivery aspects of the approach.

This guidance has been produced on behalf of the UK Operational Leads Group, and endorsed by the following partners:

- Health Research Authority, England
- Health & Social Care Research & Development (HSC R&D), Northern Ireland
- NHS Research Scotland
- Health and Care Research Wales (HCRW)

[1] This document is only applicable to amendments to project specific studies. Amendments to Research Databases and Research Tissue Banks fall outside its scope.

[2] Amendments made to a study prior to HRA and HCRW Approval or NHS R&D permission being granted should be handled as part of the permission application process.

Principles

1. The approach for management of amendments for NHS R&D offices will apply to all studies being conducted in the UK. For single-site studies, processes for managing amendments may vary slightly in different nations.
2. The approach is regarded as mandatory for all studies taking place in the UK.
3. Urgent safety measures are not covered by this new approach – urgent safety measures should be notified to all participating organisations on receipt to ensure the participants' safety. Any subsequent amendments relating to changes introduced by an urgent safety measure should be managed in accordance with this document.
4. It is expected that all amendments will be submitted with a completed and locked amendment tool via the IRAS Identity Gateway.[3]
5. This approach changes the handling of amendments to 'presumed implementation' following regulatory approval (and HRA and HCRW Approval in England/Wales), unless an objection to the amendment is raised by an HSC/NHS organisation within a reasonable time. For studies within the scope of this approach, Chief Investigator (CI)/Sponsors can presume permission for implementation of an amendment after 35 days (subject to other regulatory approvals being in place), unless the HSC/NHS organisation raises an objection within this period.
6. To support the efficient management of amendments, the approach includes a system of categorisation to allow a proportionate process to be applied. This categorisation is provided via the completed amendment tool.
7. HSC/NHS organisations considering the amendment are expected to do so in a timely manner.
    a. Where an amendment is accepted within the 35 day period, confirmation should be sent to the CI/sponsor confirming continuing participation (subject to other regulatory approvals and HRA and HCRW Approval in England and Wales).
    b. Once the 35 day period elapses, the CI/Sponsor may assume continuing participation (subject to other regulatory approvals).
8. The CI/Sponsor remains responsible for ensuring that amendments and any supporting documentation are passed to the local Principal Investigators (PIs) and their research team.

[3] Modified amendments (those in response to an unfavourable opinion from the REC of a previous amendment) and amendments to add adults who lack capacity to consent for themselves to a non-CTIMP in England and/or Wales and/or Scotland and/or Northern Ireland for the first time should not be submitted via the IRAS Identity Gateway and should be emailed to the relevant REC.

Categorisation of Amendments

Amendments have been grouped into five different categories for the purpose of handling them in a manner appropriate to the amendment.

HSC/NHS organisations should ensure the principle of these categorisations and the relevant processing of amendments is reflected in their SOPs as the MHRA will expect to see processing following the organisational SOP when conducting an inspection.

Category A - Amendment to a research study that ALL participating HSC/NHS organisations are expected to consider

This category includes any amendment to a research study that has implications for, or affects, **ALL** participating NHS organisations hosting the research study.

All participating HSC/NHS organisations will be informed of, and have access to the amendment.

All participating HSC/NHS organisations are expected to consider the amendment to determine whether it affects their capability and capacity to conduct the study or if they can continue NHS research permission.

Category B - Amendment to a research study that only those participating HSC/NHS organisations affected by the amendment are expected to consider

This category includes any amendment to a research study that has implications for, or affects, **SPECIFIC** participating HSC/NHS organisations hosting the research study.

Only those participating HSC/NHS organisations affected by the amendment will be informed of the amendment.

Only those participating HSC/NHS organisations affected by the amendment are expected to consider the amendment to determine whether it affects their capability and capacity to conduct the study or if they can continue NHS research permission.

Category C - Amendment to a research study that participating HSC/NHS organisations are not expected to consider

This category includes any amendment to a research study that has no implications that require management or oversight by the participating HSC/NHS organisations hosting the research study.

All participating HSC/NHS organisations will have access to the amendment.

Participating HSC/NHS organisations are **NOT** expected to consider the amendment but may need to update their records following any administrative changes.

Category B/C - Amendment to a research study that has aspects that some participating HSC/NHS organisations are expected to consider and other aspects that participating NHS organisations are not expected to consider

All participating HSC/NHS organisations will have access to the amendment.

Participating HSC/NHS organisations are expected to consider the amendment to determine whether it affects their capability and capacity to conduct the study or if they can give continued permission for these amendments if they are affected by the part B elements.

New Site - Amendment to a research study that only consists of new HSC/NHS sites

Only those participating HSC/NHS organisations affected by the amendment will be informed of the amendment.

New HSC/HSC sites will confirm Capability & Capacity or NHS research permission in their normal time frames.

There may be amendments of a confidential nature that the Sponsor is required to submit to the MHRA. Such amendments will have no implications for, or affect, the participating HSC/NHS organisations hosting the research study. Therefore these amendments will not be notified to the HSC/NHS organisations.

A flowchart describing the consideration of amendments according to the five different categories is shown in Appendix A.

To assist users of this document, examples of how amendments are categorised into these five different categories are shown in Appendix B. This list of examples is not intended to be exhaustive, and those responsible for quality assuring the tool should take a considered approach to this exercise. Appendix B also shows the classification of amendments into substantial and non-substantial amendments. This classification is required for Research Ethics Committee and MHRA Medicines purposes and sits alongside the categorisation for NHS R&D offices.

List of Annexes

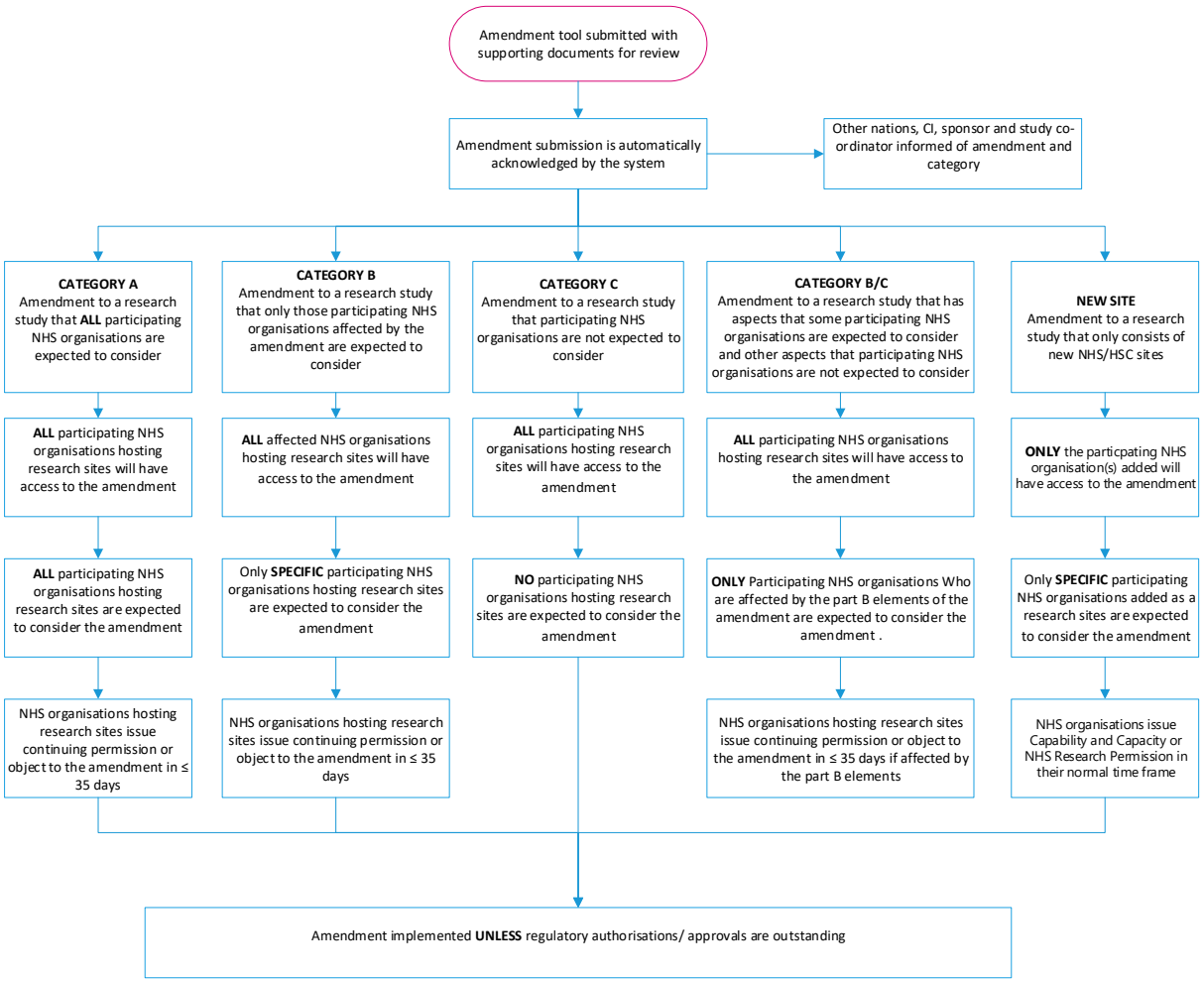
Appendix A: Amendments Categorisation flowchart

Appendix B: Examples of Amendments by Category

Appendix C: Definition of Amendments

Appendix A

Flowchart of the assessment of amendments according to the five different categories.



Appendix B

Examples of the how amendments are categorised into the five different categories.

The following table gives examples of how amendments are categorised into the five different categories, and HSC/NHS R&D offices are expected to assess the amendment in a manner appropriate to the scale of the amendment. (This list is adapted from the Standard Operating Procedures for Research Ethics Committees, Version 7.4, June 2019.)

This list of examples is not intended to be exhaustive, and those responsible for categorising amendments should take a considered approach to this exercise.

The list also shows the classification of amendments into substantial and non-substantial amendments as required for Research Ethics Committee purposes.

		R&D categorisation of amendments				**Classification of amendments**		**Study Wide Reviews Required**
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
01.	Changes to the procedures undertaken by participants.	✓				✓		✓
02.	Changes to procedures undertaken by participants with no impact on cost/ resource or risk, for example a change to interview questions.			✓			✓	
03.	Changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study.	✓				✓		✓
04.	Significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians,	✓		✓		✓		✓

		R&D categorisation of amendments				Classification of amendments		Study Wide Reviews Required
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
	information sheets for relatives or carers with impact on cost resource or risk.[4]							
05.	Minor changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers without impact on cost resource or risk. [5]	✓		✓			✓	
06.	A change to the payments, benefits or incentives to be received by participants in connection with taking part in the study.	✓				✓		
07.	Temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt.	✓				✓		
08.	Temporary halt at a study site to protect participants from harm, and the planned restart at a study site following a temporary halt.		✓			✓		
09.	Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value.			✓		✓		
10.	Changes to the design or methodology of the study, or to background information, likely to have a significant impact on	✓				✓		

[4] This change can be category A or C depending on the resource implications for sites.

[5] This change can be category A or C depending on the resource implications for sites.

		R&D categorisation of amendments				Classification of amendments		Study Wide Reviews Required
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
	procedures/ methods or resources at the research site.							
11.	A change to the definition of the end of the study.	✓				✓		
12	Extension of the study beyond the period specified in the application form.[6]	✓		✓			✓	
13.	Any other significant change to the protocol or to the terms of the application for MHRA Clinical Trial Authorisation.[7]	✓				✓		✓
14.	Any other significant change to the protocol or to the terms of the application for REC Favourable Opinion.[8]	✓				✓		✓
15.	Early closure or withdrawal of a study.	✓				✓		
16.	Early closure or withdrawal of a study site.		✓			✓		
17.	Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications.			✓			✓	
18.	Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a Chief Investigator.			✓		✓		✓
19.	A change giving rise to a possible conflict of interest on the part of the Chief Investigator.		✓[9]			✓		

[6] An extension can be category A or category C depending on whether it will require additional resources at sites.

[7] Except for those that have been previously seen by the participating NHS organisations, e.g. Urgent Safety Measures.

[8] Except for those that have been previously seen by the participating NHS organisations, e.g. Urgent Safety Measures.

[9] This specific to the Chief Investigator's NHS organisation only. It is the responsibility of the Chief Investigator's employing organisation to inform the Sponsor of the any conflict of interest.

		R&D categorisation of amendments				Classification of amendments		Study Wide Reviews Required
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
20.	Appointment of a new Principle Investigator, or temporary arrangements to cover the absence of a Principle Investigator.[10]		✓			✓	✓	
21.	A change giving rise to a possible conflict of interest on the part of any Principal Investigator or Local Collaborator.		✓			✓		
22.	A change to the payments, benefits or incentives to be received by researchers in connection with taking part in the conduct of the study.	✓				✓		✓
23.	Changes to the radiation dose given to a participant taking part in a study.	✓				✓		✓
24.	Changes to the requirements of an ARSAC certificate at a research site.		✓			✓		✓
25.	Minor changes in the logistical arrangements for storing or transporting of samples.			✓			✓	✓
26.	Significant changes in the logistical arrangements for storing or transporting of samples	✓				✓		✓
27.	Issue of an updated Investigator's Brochure or Summary of Product Characteristics relating to an investigational medicinal product.[11]			✓			✓	

[10] This is a Substantial Amendment for a CTIMP and a Non-substantial amendment in a non-CTIMP.

[11] It is important that a copy of updated Investigator's Brochure or Summary of Product Characteristics is supplied to the pharmacy department at the research site.

		R&D categorisation of amendments				Classification of amendments		Study Wide Reviews Required
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
28.	A change of Sponsor(s) or Sponsor's legal representative.	✓				✓		✓
29.	Changes to contact details for the Sponsor (or the Sponsor's representative), Chief Investigator or other project staff.			✓			✓	
30.	A change in the contact details of the insurer to the continuing insurance arrangements for the study.			✓		✓		
31.	A temporary halt/ stop to the insurance or indemnity arrangements for the study.	✓				✓		✓
32.	Changes in funding arrangements: the contact details of the funder.			✓			✓	
33.	Changes in funding arrangements: the funding envelope (i.e. the availability of funding to support the research study).	✓				✓		✓
34.	In a Clinical Trial of Investigational Medicinal Product (CTIMP), addition of a new site not listed in the original application.				✓[12]	✓[13]		✓
35.	In a non-CTIMP, addition of any new NHS site.				✓[14]		✓	✓
36.	Changes to a research study following an urgent safety measure.			✓		✓		✓

[12] Where the amendment is the addition of a new research site, the application for a new research site should proceed through the NHS permission process appropriate to the addition of a new research site in accordance with the requirements of the nation where the new research site is to be added.

[13] If the site was not included in the list of proposed trial sites in the original REC application, then the applicant must submit a substantial amendment to the REC only. There is no requirement to notify the MHRA.

[14] Where the amendment is the addition of a new research site, the application for a new research site should proceed through the NHS permission process appropriate to the addition of a new research site in accordance with the requirements of the nation where the new research site is to be added.

		R&D categorisation of amendments				Classification of amendments		Study Wide Reviews Required
Nº	**Amendment**	**Category A**	**Category B**	**Category C**	**New Site**	**Substantial**	**Non-substantial**	
37.	Change in the Project Identification (e.g. change of title, reference numbers).			✓			✓	
38.	Change to confidential patient information arrangements.	✓				✓		✓
39.	Addition of Participant Identification Centres for the first time, or a change to activities undertaken by existing PICs.	✓					✓	✓
40.	Addition of Participant Identification Centres undertaking the same activities as existing PICs.				✓		✓	
41.	GDPR wording - Unaccepted alternative wording used.[15]			✓			✓	✓

[15] If Accepted GDPR wording is used this is a non-notifiable amendment.

Appendix C: Definition of Amendments

A “substantial amendment” is defined as an amendment that is likely to affect to a significant degree any of the following:

(a) the safety or physical or mental integrity of the subjects of the trial,

(b) the scientific value of the trial,

(c) the conduct or management of the trial, or

(d) the quality or safety of any investigational medicinal product used in the trial.

Para. 6.3, Standard Operating Procedures for Research Ethics Committees, Version 7.4, June 2019. National Research Ethics Service, Health Research Authority.

A non-substantial amendment can be defined as an amendment that is not a substantial amendment.

For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial. Any valid amendment submitted as a substantial amendment should be accepted for review. Equally, if the sponsor is satisfied that an amendment is not substantial, there is no requirement to notify the REC although non-substantial amendments may be notified for information only at the sponsor’s discretion.

Para. 6.22, Standard Operating Procedures for Research Ethics Committees, Version 7.4, June 2019. National Research Ethics Service, Health Research Authority.

A sub-set of non-substantial amendments are ‘non-substantial, no study wide review required amendments’. These amendments do not require any regulatory or governance review. They should be submitted for information and implemented in accordance with the categorization information in the amendment tool.