STANDARD OPERATING PROCEDURE 6
Amendments to Approved Study Documents

Version:	6.0	Effective Date:	12 September 2023
Issue Date:	29 August 2023	Review Date:	12 September 2023
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Revision Chronology:	Effective date:	Reason for change:
Version 6.0	12 September 2023	Biennial review: Addition of process flowcharts. Other minor updates to text to reflect current procedures.
Version 5.0	13 May 2021	Minor amendment to reflect changes to HRA guidance on: i) the addition of new sites/PIs in CTIMPs which will no longer be considered a substantial amendment and ii) notifications to the MHRA can now be done using the amendment tool in place of the Annex 2 form.
Version 4.0	3 December 2020	Creation of new SOP specifically to detail processes for submission and approval of amendments to approved study documents. The information previously detailed in this SOP regarding initial approval procedures can now be found in SOP 5 part 1 for applications to an Ethics Committee, SOP 5 part 2 for applications to the MHRA (regulatory approvals) and SOP 5 part 3 which details ongoing communication requirements.
Version 3.1	24 February 2020	Biennial review: Updates to required documentation for approvals, updated application process flowchart QA requirement to review all amendments to WCTU studies. Change to new format
Version 3.0	1 December 2017	Updated to include new HRA approvals procedures including NHS Trust permissions.
Version 2.3	1 February 2016	Biennial review: Web links updated (HRA). Changes to REC booking procedure. Addition of requirements for trial registration, electronic authorisations and amendment notifications for NIHR funded projects.
Version 2.2	15 August 2013	Biennial review: Process flowcharts and web links updated. Minor text changes.
Version 2.1	21 March 2011	New guidance on notifying protocol amendments (section 3.3.2). Addition of Appendix 1.
Version 2.0	21 May 2010	Update of SOP to reflect new application system (IRAS). Remove information on R&D approval process to create new SOP.
Version 1.1	31 January 2008	Change references from COREC to NRES. Changes to application processes, to include process for amendments detailed.
Version 1.0	March 2006	

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1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to describe the processes required to amend previously approved research study documents and obtain relevant approvals from NHS Research Ethics Committees (REC), the Health Research Authority (HRA), the UK's Regulatory Authority, the Medicines and Healthcare products Regulatory Agency (MHRA) and other bodies e.g., Confidentiality Advisory Group (CAG).

It is applicable to any researcher working on a Warwick sponsored research study or for studies managed by WCTU sponsored by external organisations where use of Warwick SOPs has been agreed.

2. Definitions

Approval	The affirmative decision of the REC or Regulatory Authority that the study has been reviewed and may be conducted at the institution site within the constraints set forth by the REC, MHRA (as applicable), the institution and Good Clinical Practice (GCP) requirements.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study.
Protocol Amendment	A written description of change(s) to, or formal clarification of, a protocol.
Essential Documents	Documents which (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been, conducted in accordance with the applicable regulatory requirements.
Substantial amendment*	A change to the terms of the REC and/or MHRA application, the protocol or any other document submitted with the application, which significantly affects one of the following: • The safety or physical or mental integrity of study participants • The conduct or management of the study • The scientific value of the study • The quality or safety of any investigational medicinal product used in the study
Non-substantial amendment*	A change to the conduct of the clinical trial that does not have a significant impact on the safety of the subjects, the scientific value of the study or study conduct i.e., minor changes which do not meet the definition of substantial.
Research Ethics Committee (REC)	An independent body constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a study.
Medicines and Healthcare products Regulatory Agency (MHRA)	The MHRA is the UK regulator of medicines, medical devices and blood components (known as the UK's Competent Authority within clinical trial legislation). They are responsible for ensuring

	the safety, quality and effectiveness and approval of all clinical trials of Investigational Medicinal Products (IMP).
Health Research Authority (HRA)	An extension of the Department of Health in the UK. The HRA manage the UK NHS Research Ethics Committees.

* Examples of substantial and non-substantial amendments can be found in Appendix 1

3. Background

Once initial applications for a study have been approved (See SOP 5; Part 1 for REC/HRA approvals and Part 2 for MHRA approvals) and the study is being conducted, it is not uncommon for the trial procedures detailed in the protocol or for other essential documents (e.g., Participant Information Leaflets) to require amending to reflect best practice or new information.

Substantial changes to a research protocol or other documents or study procedures must obtain HRA/ethical approval (and MHRA/other approvals as applicable) **before** the proposed amendments can be implemented (unless the change is required to deal with an urgent safety measure – see SOP 17 part 3 'Urgent Safety Measures' for full details).

4. Procedure

4.1 Responsibilities

Chief Investigator (CI)	• Making amendment applications to the relevant authorities. This can be delegated but CI must retain responsibility for content.
Research Sponsor(s)	• Assess whether an amendment is 'substantial' on a case-by-case basis and confirm their opinion with the CI prior to submission. • Review and sign amendment tool prior to locking for submission.

4.2 When?

Written approval must be obtained from the HRA before an amendment to a previously approved document can be implemented at research sites.

Where an amendment is relevant to a study recruiting site within the NHS, management assessment by the local NHS Research & Development (R&D) office at each site to confirm their continuing capacity and capability to conduct the study should be confirmed, or if there are no objections from the R&D officers, the amendment can be implemented after 35 days (R&D teams can request an extension to this 35 day period but only if it's justified and notice is provided to the coordinating centre).

4.3 How?

Submission of amendment documents are made using the Integrated Research Application System (IRAS) which is accessed via: https://www.myresearchproject.org.uk/. Full details of how to submit the amendment tool and supporting documents can be found here.

4.3.1 Making an amendment

All applicants making an amendment (whether substantial or non-substantial) to project-based research will need to complete the amendment tool and submit their amendment online.

For amendments to CTIMPs approved via the combined review process which uses a separate part of IRAS, the amendment tool should also be used using the same process as for non-CTIMPs instead of the EudraCT Annex 2 amendment form. However, use of the Annex 2 form is still permitted for submission of 'bulk' amendments (i.e., identical changes to multiple studies at one time). All CTIMPs submitted through the combined review service via the new part of IRAS, should consult the guidance available here.

All amendments to Warwick sponsored trial documents must be forwarded to the Sponsor's Office (via sponsorship@warwick.ac.uk) to obtain the sponsor's assessment on whether the amendment is considered to be substantial or not. Amendments to studies sponsored by external sponsors must be dealt with in accordance with their sponsor's requirements.

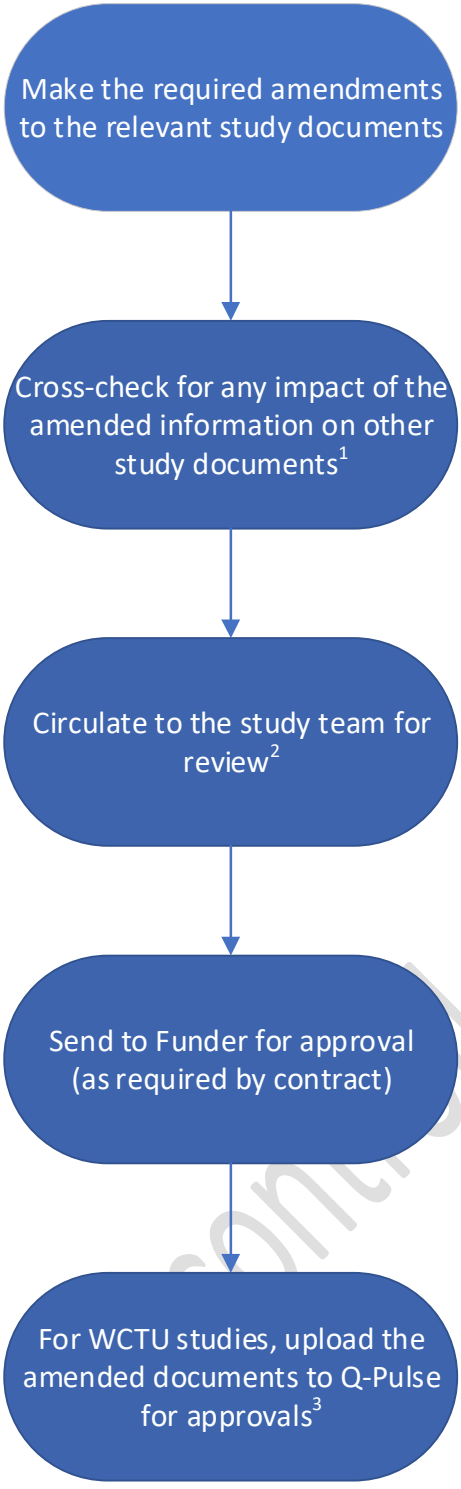
For CTIMPs and clinical investigations of medical devices only, substantial amendments should also be notified to the REC *prior to the start of the study* where significant changes are requested by the MHRA as part of the initial regulatory approval process and these changes are relevant to ethical review.

Under normal circumstances, substantial amendments require favourable opinion from the main REC/HRA/MHRA (as applicable) before implementation. The only exceptions to this are:

- Urgent Safety Measures (see SOP 17 part 3: Urgent Safety Measures)
- CTIMP amendments which only require authorisation by the MHRA

4.3.1.1 Preparation and Submission of amendments

Step 1 - Amend the relevant study documents:



1. The study management team should ensure that an impact assessment is carried out on all key study documents e.g., protocol, CRFs, data management plan, SAP, Risk Assessment and Monitoring Plan to check if any associated documents require amending based on the proposed amendments to the study.

2. For WCTU managed studies, all substantial amendment documentation must be forwarded to the WCTU QA Team for review.
Study statisticians should review all protocol amendments to determine any change of impact to statistical elements of the study. Trial Managers/Coordinators should communicate the nature of the amendment to their statistician and document the decision to exclude them from the review/approval process if applicable e.g. on an email, in Trial Management Group (TMG) minutes or Note to File.

3. For WCTU managed studies where a team member does not have access to Q-Pulse, an email confirming their approval should be sent (following **G33** guidance on email approvals available from https://warwick.ac.uk/fac/sci/med/research/ctu/ctuintranet/qa/templates) and saved in the TMF

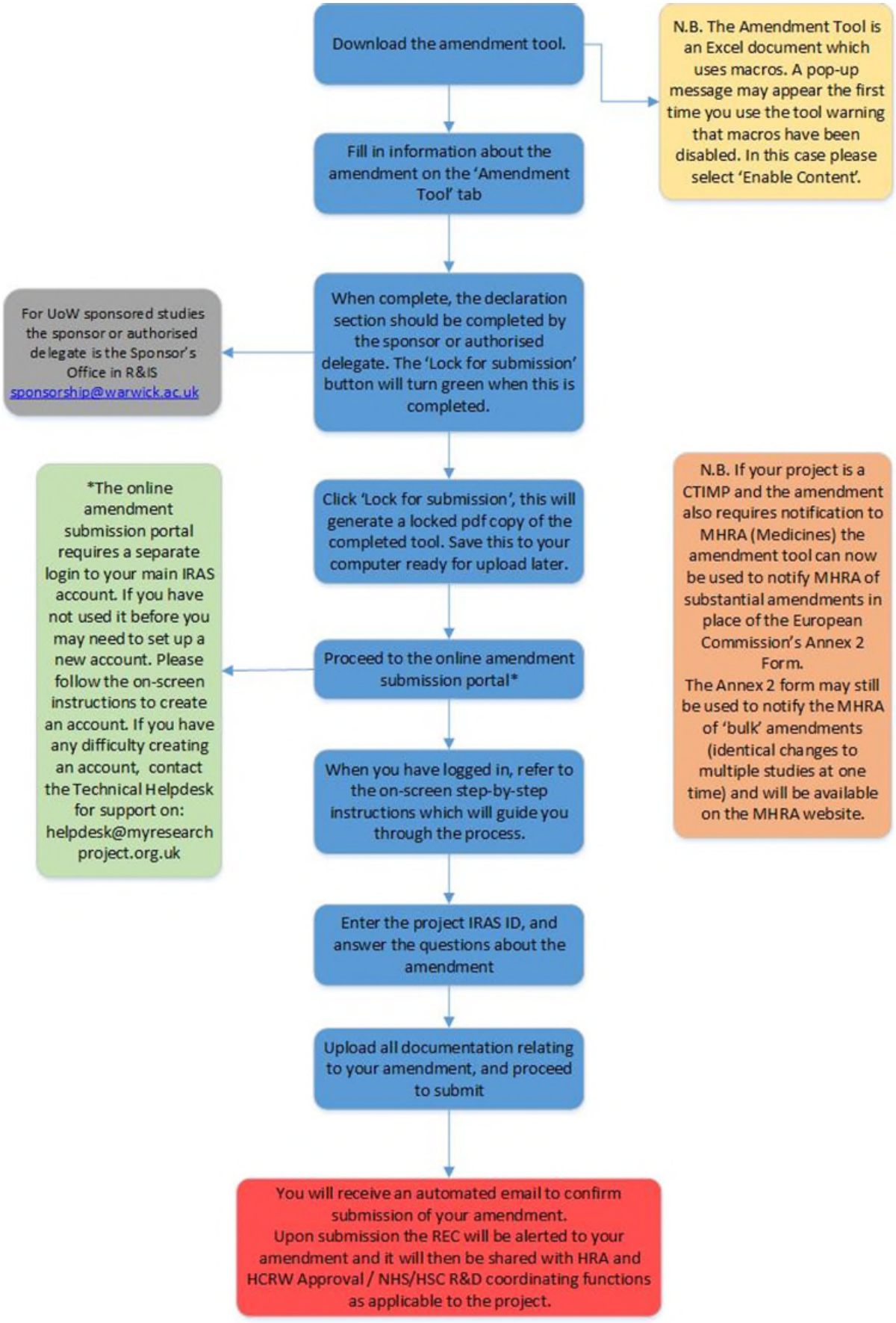
For studies managed outside of WCTU, ensure all relevant team members have had an opportunity to review and subsequently approve the amended documents and that their approval emails are saved.

Step 2: Complete the Amendment Tool:

It is important to use the current version of the amendment tool which can be downloaded from the IRAS Help section on Amendments

The Amendment Tool applies to all project-based research which are defined as any of the IRAS Project Filter question 2 categories, except for Research Tissue Banks (RTBs) and Research Data Bases (RDBs) who continue to use the Notice of Substantial Amendment Form generated in IRAS to notify substantial amendments to the REC. For all types of research, amendments and supporting documentation should be uploaded and submitted for review via online submission.

The process for completing the amendment tool is as follows:


Download the amendment tool.
N.B. The Amendment Tool is an Excel document which uses macros. A pop-up message may appear the first time you use the tool warning that macros have been disabled. In this case please select 'Enable Content'.
Fill in information about the amendment on the 'Amendment Tool' tab
When complete, the declaration section should be completed by the sponsor or authorised delegate. The 'Lock for submission' button will turn green when this is completed.
For UoW sponsored studies the sponsor or authorised delegate is the Sponsor's Office in R&IS sponsorship@warwick.ac.uk
Click 'Lock for submission', this will generate a locked pdf copy of the completed tool. Save this to your computer ready for upload later.
N.B. If your project is a CTIMP and the amendment also requires notification to MHRA (Medicines) the amendment tool can now be used to notify MHRA of substantial amendments in place of the European Commission's Annex 2 Form.
The Annex 2 form may still be used to notify the MHRA of 'bulk' amendments (identical changes to multiple studies at one time) and will be available on the MHRA website.
Proceed to the online amendment submission portal*
*The online amendment submission portal requires a separate login to your main IRAS account. If you have not used it before you may need to set up a new account. Please follow the on-screen instructions to create an account. If you have any difficulty creating an account, contact the Technical Helpdesk for support on: helpdesk@myresearchproject.org.uk
When you have logged in, refer to the on-screen step-by-step instructions which will guide you through the process.
Enter the project IRAS ID, and answer the questions about the amendment
Upload all documentation relating to your amendment, and proceed to submit
You will receive an automated email to confirm submission of your amendment.
Upon submission the REC will be alerted to your amendment and it will then be shared with HRA and HCRW Approval / NHS/HSC R&D coordinating functions as applicable to the project.

NOTES:

- Though the CI is not required to sign the amendment tool, it is good practice to copy them into the email to the sponsor when requesting approval.
- When uploading the supporting documents, it is recommended that the save button is pressed after uploading each document in case the system crashes to prevent losing what has been uploaded. It is good practice to submit both tracked changes and clean new version of each document for ease of review.
- Study recruitment sites who will be affected by the amendment can be informed that an amendment has been made and submitted to begin the 35-day count down for any objections or requests for further information.
- Where the amendment is in relation to the addition of new recruitment sites or Participant Identification Centres (PICs), the Local Information Pack (LIP) should not be sent until the amendment for their inclusion has been approved.
- Where the amendment could significantly affect the scientific value of the research, further evidence of scientific and/or statistical review should be provided.
- A covering letter should also be produced and uploaded to detail which documents are included in the submission and a summary of the changes made.
- Further amendments can be made (if they are regarding different documents) whilst a previous submission is ongoing if necessary, however, this is not recommended as very close management of the submissions would be required.
- Studies which involve participants who lack capacity and have sites in Scotland as well as in England, Wales and Northern Ireland, will need to complete two separate amendment tools; one for the Scottish REC and another for the English REC (which covers Wales and N. Ireland). A separate IRAS number will be needed for the Scottish REC submission.
- It is no longer necessary to have separate PIS and consent forms for Northern Ireland. Northern Irish RECs accept PIS and consent form documents used for the English sites.

4.3.1.2 Amendment classifications

The completed Amendment Tool will output the recommended amendment category automatically based on your responses to the questions. It is important to ensure the correct selections are made on the form to ensure the correct category is allocated.

The categories are listed in the table below.

Category:	This category includes any amendment to a research project that has:
A	Implications for, or affects, all participating NHS/HSC organisations hosting the research project.
B	Implications for, or affects, specific participating NHS/HSC organisations hosting the research project. (Category B amendments do not need to be shared with organisations that are not affected by it).
C	No implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However, the amendment should still be provided for information even though no capacity or capability review is required by participating organisations.. *Note - Updated Investigator Brochure (IB; Clinical Trials of Investigational Medicinal Products (CTIMPs) only):* Where the IB update, annual or otherwise, constitutes a non-substantial amendment for REC and MHRA and this is the only amendment (e.g. the update to IB does not give rise to updated pharmacy manual or protocol) the updated IB should not be submitted for categorisation. These amendments will always be category C and they will not be

	assessed by NHS/HSC if submitted. The IB should be provided to each participating NHS/HSC organisation.
Non-notifiable	Amendments for minor changes only e.g., typos or to translations of documents will be classed as non-notifiable i.e., there is no need to make an online submission for review. However, affected NHS/HSC organisations should be informed about the amendment.

4.3.1.3 Sharing amendment documentation

There is detailed information on sharing amendments with participating organisations on IRAS.

Participating NHS organisations in England and/or Wales:

After submission of an amendment, share your completed Amendment Tool with confirmation of amendment category and, if applicable, amended documents together with all relevant participating NHS organisations in England and/or Wales impacted by the amendment. It is good practice to add an 'unapproved' water mark to amended documents at this stage.

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

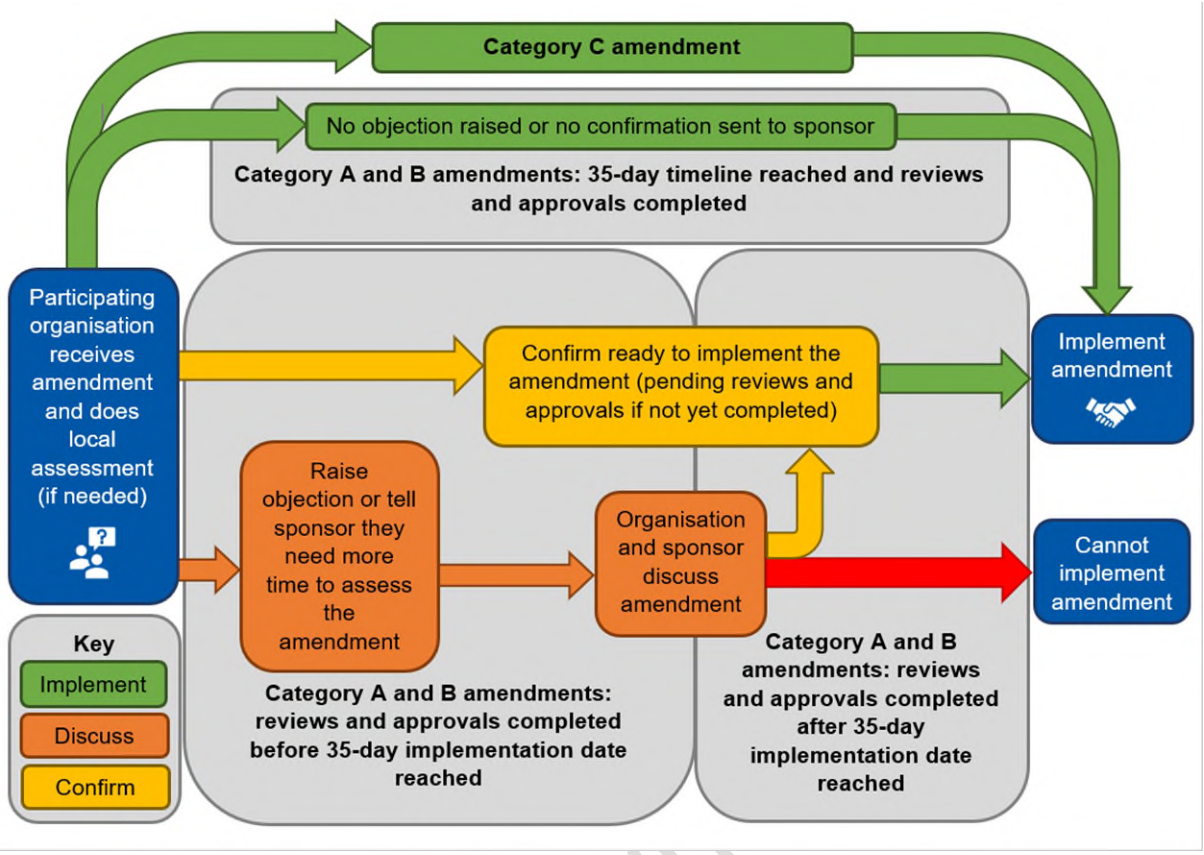
There are template emails available via IRAS which can be used when notifying NHS organisations of an amendment and to confirm when an amendment can be implemented.

In Northern Ireland and/or Scotland:

For multicentre studies there is no need for you to send the amendment to R&D offices of participating organisations in these nations as the National Coordinating Function will pass this on to them along with any amended documents on your behalf.

Single centre study amendments should be sent directly to the R&D team at the participating organisation.

The tool and amended documents should be shared with the research teams at relevant participating NHS/HSC organisations in Northern Ireland and/or Scotland who should then prepare to implement the amendment.



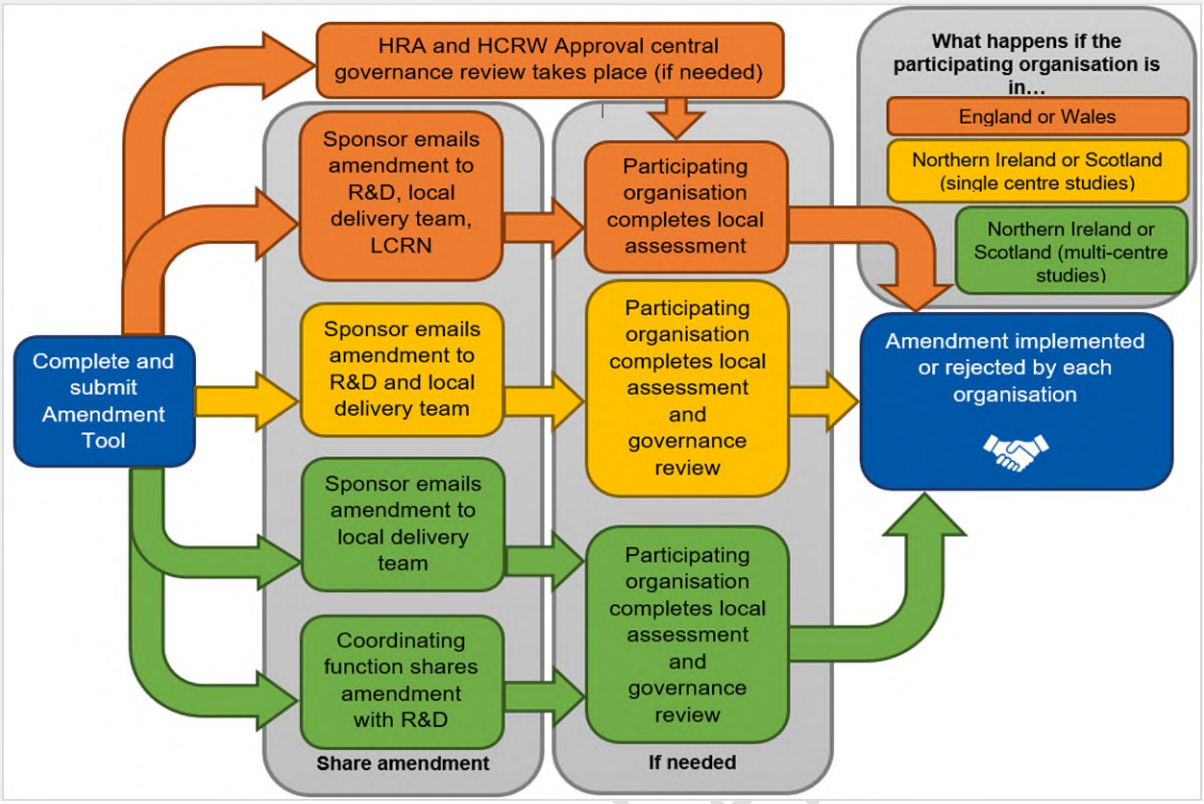
4.3.1.4 Outcomes

The REC/HRA/MHRA (as applicable) will review the amendment and pass on their opinion.
There are 3 possible outcomes:

1. Unfavourable opinion	**Return to the start of the process and resubmit**
2. Favourable opinion no further review from HRA required	Applicants should communicate this to sites (both the research team and the R&D office), and the local CRN. If any amendments are category A or B, sites have 35 days to raise any objections, after which if no objections have been raised, the amendment can be implemented. For Category C amendments, applicants will be sent an email from the system to state that the amendment can be implemented immediately; no further approval will be received.
3. Favourable opinion further assessment needed	Applicants will receive an email following further evaluation, after which the same process of notification as above should be followed.

4.3.1.5 Implementing amendments in participating NHS/HSC organisations

There are detailed instructions on IRAS relating to the implementation of amendments which is important to follow, particularly where study sites are in the devolved nations, as the processes for England and/or Wales differ from those for Scotland and/or Northern Ireland.



The following points apply to NHS/HSC organisations in all nations:

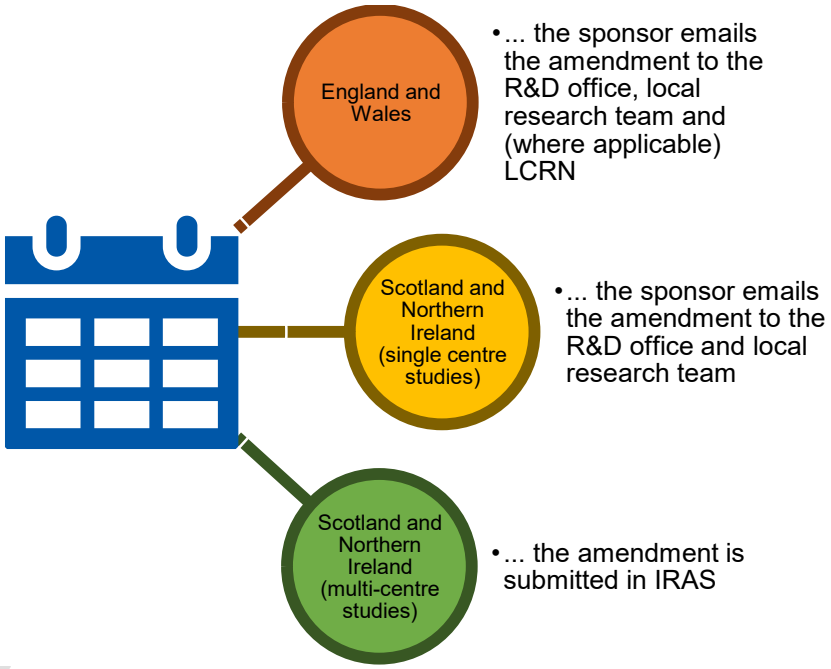
- Sponsors should not expect to receive a letter or email of confirmation from NHS/HSC organisations before implementing the amendment.
- If all relevant regulatory approvals are in place and there has been no objection from site, the amendment can be implemented after 35 days (though sites may request an extension to the 35-day period if necessary).
- Category A and B amendments may be implemented sooner than 35 days in cases where all regulatory approvals have been issued and where the NHS/HSC organisation has confirmed that the amendment may be implemented prior to this date.
- Upon receipt of the amendment, the coordinating function of the lead nation will share the amendment with the coordinating function of any other participating nation(s). There is no need to separately submit to each nation.

Once you have notified participating NHS organisations in **England and/or Wales** of the amendment, they should prepare to implement the amendment. The amendment may then be implemented at all participating NHS organisations in England and/or Wales **35 calendar days** from the day on which the organisation(s) were provided with the amendment and any amended documents; so long as all three of the following conditions are satisfied:

1. HRA and HCRW Approval has been issued (where required)	2. A participating NHS organisation does not request additional time to assess	3. A participating NHS organisation declines to implement the amendment
Where approval is pending, you should not implement.	Don't implement until they are ready to do so.	Discuss and take appropriate actions in agreement with the NHS organisation.
If HRA and HCRW Approval is issued after the 35 day deadline, you may implement	Work with the organisation to resolve any outstanding issues.	

When approval is received you may implement the amendment at all participating NHS/HSC organisations in Northern Ireland and/or Scotland 35 days after organisations have received the amendment and all supporting documentation as long as the conditions stated above for England and/or Wales are met.

35-day implementation period begins when:



4.3.2 Support

For England and Wales led studies: amendments@hra.nhs.uk

For Scotland led studies: Gram.nrspcc@nhs.scot

For Northern Ireland led studies: Research.Amendments@hscni.net

Amendment submission portal – technical queries: helpdesk@myresearchproject.org.uk

Amendment content or classification: Direct to the relevant Sponsor's Office or the REC that issued favourable opinion for the study.

N.B. Flag in the email subject that your query relates to the Amendment Tool so that it can be identified and handled efficiently.

4.3.3 Modified Amendments after an unfavourable opinion

Where the REC gives an unfavourable opinion of a substantial amendment, the sponsor or CI may submit a modified amendment taking account of the Committee's concerns. In this case a new amendment tool should be completed, following the process flowchart above, indicating that it relates to a modified amendment at the relevant question. It should then be submitted directly to the REC alongside all supporting documentation by email. All documents revised for approval after an unfavourable opinion must be reviewed and approved and given a new version number.

Modified amendments must not be submitted using the online portal. REC email addresses can be found on the HRA website.

4.3.4 Submission of Substantial Amendments to the MHRA (CTIMPs)

Only substantial amendments need to be submitted to the MHRA and full guidance about procedures for notifying substantial amendments to the MHRA, is available via https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues or https://www.myresearchproject.org.uk/help/hlpamendments.aspx

Note, that amendments unrelated to the MHRA CTA only need submission for approval to the REC.

4.3.5 Notifying amendments to MHRA Devices

The following guidance applies to amendments to clinical investigations of medical devices subject to regulation by the Competent Authority.

You must notify MHRA Devices of **all** proposed changes to the investigation (not only those classified as substantial amendments for the purposes of ethical review) and await a letter of no objection from MHRA Devices before you implement them. This includes changes made at the request of the REC. Failure to notify proposed changes could result in the manufacturer being liable to prosecution.

When notifying MHRA of changes, provide the following information in writing:

- the MHRA reference number for the trial
- details of the proposed change(s) to the clinical investigation plan or the design of the device
- the reason for the change(s); and
- 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.

Notifications should be sent directly to MHRA Devices. Details of where to send notifications can be found on the MHRA website at: https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

4.3.6 Amendments to add the involvement of Adults Lacking Capacity for the first time

Because of the specific REC review requirements, it is not possible for this type of amendment to be submitted via the online portal.

The type of amendment and level of information you need to provide will vary depending on the location of the lead nation and nation/s where the amendment will be implemented. You should therefore contact the REC that originally issued favourable opinion for the study flagging in your covering email that the amendment involves Adults Lacking Capacity being added to the study for the first time. They will be able to advise on any additional steps you need to take. REC email addresses can be found on the HRA website.

4.3.7 Submitting amendments to the Confidentiality Advisory Group (CAG)

CAG should be notified of all amendments to the information provided in your original application. (Details of how to make an initial application to CAG can be found in SOP 43 Seeking and Maintaining Approval from the Confidentiality Advisory Committee (CAG).

This is because support to process confidential patient information without consent is based on the precise details originally provided to CAG and so any change will **not** be covered by the existing support until a formal amendment is made and the amendment is supported.

You will need to complete and submit an amendment form to CAG where changes are intended to any of the following:

- Data flows
- Data items
- Data sources
- Purpose of application
- Data controller (please note that an amended application form and supporting documents setting out the new data controller arrangements will be required, you are advised to contact the Confidentiality Advice Team prior to submission)
- Data processor
- Duration amendment

Guidance on submitting amendments to CAG is available on the IRAS help pages

If you are unsure whether an amendment needs to be submitted after reviewing the template and/or need further guidance, contact the Confidentiality Advice Team (CAT):
Email: cag@hra.nhs.uk
Phone: 020 7972 2557
The CAT may advise that you submit the amendment for information only at this stage.

Once you have submitted the completed amendment form the Confidentiality Advice Team will confirm if the amendment contains sufficient information, whether it is valid and the process and timelines for its review. You may be asked to provide further information prior to confirmation that your amendment is valid.

If the amendment can be reviewed outside a full CAG meeting an outcome should be provided within 30 days of receipt of a valid amendment, if the amendment is referred to a full CAG meeting an outcome can be expected within 60 days of receipt of a valid amendment. The Confidentiality Advice Team will inform you if your amendment is referred to a full CAG meeting. That final approval for the amendment will not come into effect until a final approval letter is issued. The possible outcomes of the review of the amendment are that the amendment is:

- Fully supported

- Conditionally supported
- Not supported

List of abbreviations

CAG	Confidentiality Advisory Group
CAT	Confidentiality Advice Team
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HSC	Health & Social Care
IB	Investigator Brochure
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
LCRN	Local Clinical Research Network
LIP	Local Information Pack
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIC	Patient Identification Centre
QA	Quality Assurance
RDB	Research Data Base
RTB	Research Tissue Bank
R&D	Research and Development
R&IS	Research and Impact Services
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
WCTU	Warwick Clinical Trials Unit

APPENDIX 1: Examples of substantial/non-substantial amendments

The examples below are documented in the European Commission document – 'Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of trial'. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF

The HRA website also provides a list of typically substantial/non-substantial amendments: http://www.hra.nhs.uk/resources/after-you-apply/amendments/substantial-and-non-substantial-amendments/

Examples of protocol amendments that are typically 'substantial':

Substantial Amendment	Normally requiring a favourable REC opinion only	Normally requiring MHRA authorisation only	Normally requiring both authorisation and a favourable REC opinion
a) Change of main objective of the trial, or to background information affecting its scientific value			✓
b) Change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the trial			✓
c) Use of a new measurement for the primary endpoint			✓
d) New toxicological or pharmacological data or new interpretation of this data which is likely to impact on the risk/benefit assessment			✓
e) A change in the definition of the end of the trial, even if the trial has in practice already ended			✓
f) Addition of a trial arm or placebo group			✓
g) Change of inclusion or exclusion criteria, such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the trial			✓
h) For non-CTIMPs, changes to the procedures undertaken by participants; any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study	✓		

Substantial Amendment	Normally requiring a favourable REC opinion only	Normally requiring MHRA authorisation only	Normally requiring both authorisation and a favourable REC opinion
i) Reducing the number of monitoring visits		✓	
j) Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the trial			✓
k) Withdrawal of an independent data monitoring board			✓
l) Change of IMPs			✓
m) Change of dosing of IMPs			✓
n) Change of mode of administration of IMPs			✓
o) Changes to the reference safety information or IMP dossier		✓	
p) A change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit analysis			✓
q) Significant changes to the study documentation e.g., PIS, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers	✓		
r) Change of sponsor(s) or sponsor's legal representative			✓
s) Appointment of a new CI	✓		
t) A change to the insurance or indemnity arrangements for the study	✓		
w) Temporary halt of a trial to protect participants from harm, and the planned restart following a temporary halt			✓
x) Significant changes to recruitment or consent procedures, including the	✓		

Substantial Amendment	Normally requiring a favourable REC opinion only	Normally requiring MHRA authorisation only	Normally requiring both authorisation and a favourable REC opinion
inclusion of adults lacking capacity in the trial			
y) Any other significant change to the protocol or terms of the REC application.	✓		

Examples of protocol amendments that are typically 'not substantial':

Amendments not normally requiring notification
a) Changes to the identification of the trial (e.g., change of title etc.)
b) The addition/deletion of exploratory/tertiary endpoints
c) A minor increase in the duration of the trial (<10% of the overall time of the trial)
d) An increase in duration of > 10% of the overall time of the trial, provided that: **- the exposure to treatment with the IMP is not extended** **- the definition of the end of the trial is unchanged, and** **- monitoring arrangements are unchanged**
e) A change in the number of clinical trial participants per trial site, if the total number of participants is identical or the increase/decrease is insignificant in view of the absolute number of participants
f) A change in the number of clinical trial participants in total, if the increase/decrease is insignificant in view of the absolute number of participants
g) A change in documentation used by the research team for recording study data collected directly from participants
h) Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis
i) Minor clarifications or changes to the protocol or to other trial documentation
j) Correction of typographical errors
k) Updates to the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial)
l) Changes in funding arrangements
m) Inclusion of new sites and investigators in trials other than CTIMPs
n) Any change of persons other than the sponsor (or sponsor's legal representative), at the coordinating centre or at trial sites; for example, applicant, clinical research associates, clinical research organisations

Amendments not normally requiring notification
o) Any change to the contact details of persons referred to in the documentation (N.B. even though this is not considered as a substantial amendment, the MHRA should be informed of such a change as soon as possible)
p) Changes to the internal organisation of the sponsor or of the persons to whom certain tasks have been delegated
q) Changes in logistical arrangements for storing/transporting samples
r) Change of technical equipment
s) Inclusion of a new trial site (not listed in the original application) in a CTIMP
t) Appointment of a new Principal Investigator at a trial site in a CTIMP