

SOP-QA-19 V6

Title: Amendments

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GRAMPIAN CLINICAL RESEARCH OFFICE



Document History

Version	Description of update	Date Effective
5	Change of author Updated to reflect IRAS online submission of amendments 3.5 – 3.29	9-7-20
6	Clarification that this SOP does not cover amendments in MDCI at 1.1 Inclusion of non-notifiable amendment at 3.1 and 3.4 Reference to trials submitted to insurers for agreement at 3.7 Clarification of Non-notifiable, Non-substantial and Substantial amendments 3.10 – 3.19 Clarification of MHRA reporting at 3.20 Reference to Medical Information form at 3.21 Reference to combined review service 3.22-3.29	9-7-23

1. Scope

1.1 This SOP applies to any individual participating in a research project sponsored or co-sponsored by University of Aberdeen (UoA) and/or NHS Grampian (NHSG) and delegated the task of preparing and obtaining approval for amendments to the protocol, essential documentation or other aspect of a study's arrangements.

⚠ This SOP does not cover amendments in Medical Device Clinical Investigations (MDCI). For advice on MDCIs please contact Research governance: researchgovernance@abdn.ac.uk.

1.2 ⚠ Approval from Sponsor must be obtained **prior** to submitting any amendment to the Research Ethics Committee (REC) and/or Medicines and Healthcare products Regulatory Authority (MHRA) and NHS R&D.

2. Responsibilities

Chief Investigator (CI) Request authorisation of all amendments from Sponsor, ensure all documents are subject to version control and are filed in the Trial Master File (TMF).

Research Governance Ensure that insurance is still in place after any amendment.

3. Procedure

Classification of Amendments

3.1 Amendments are classified as substantial, non-substantial or non-notifiable.

3.2 A **substantial** amendment is defined as a change to the protocol or any other supporting documentation (eg participant information sheet, participant consent form), that is likely to affect to a significant degree any of the following:

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- The safety, physical or mental integrity of the participants.
- The scientific value of the study.
- The conduct or management of the study.
- The quality or safety of any investigational medicinal product (IMP) used.

3.3 A **non-substantial** amendment is defined as a change to the details of the study which will have no significant implications for participants, the scientific value, conduct or management of the trial, or quality and safety of the Investigational Medicinal Product in a CTIMP.

3.4 A **non-notifiable** amendment is defined as an amendment that does not require online amendment submission (via the IRAS online amendment portal) for review. Affected participating organisations should be informed about the amendment.

❗ Examples of substantial amendments, non-substantial amendments and non-notifiable amendments are listed in Appendix 1.

Requesting Authorisation of Amendments from the Sponsor

3.5 For research studies sponsored or co-sponsored by the UoA and/or NHSG, the CI, or delegate, shall notify the Sponsor, via email to the Research Governance Team (RGT) of their intention to make an amendment.

3.6 All amendments for research projects (with the exception of tissue bank and research databases) shall use the IRAS Amendment Tool. The Amendment Tool and full guidance on its use can be found at <http://www.myresearchproject.org.uk/help/hlpamendments.aspx>

3.7 The tool should be downloaded from IRAS and completed using the on-screen guidance notes. Once complete it should be emailed with any amended documents to the RGT. The RGT shall review the amendment documentation and discuss and agree the amendment with the CI, or delegate, as necessary. Whilst reviewing any amendment the RGM, or delegate, shall consider if it alters the risk of the study. Any amendment which is considered to potentially increase the risk by a significant degree shall be sent to the Clinical Studies Oversight Group (CSOG) and where applicable to the insurer for an opinion prior to Sponsor authorisation.

❗ Where the changes to a study are deemed to increase risk, the study specific risk assessment shall be reviewed and updated. If required, a summary of all other significant amendments not considered to significantly increase risk, will be provided to CSOG.

❗ For trials that are specifically submitted to the insurers for their agreement (ie if the trial initially fell into the referral criteria and was passed to the insurer for their agreement, or if an amendment moves it into the referral criteria) subsequent amendments of the protocol shall be referred to the insurer by Sponsor, as appropriate, to confirm continued insurance cover and ensure that the current version is noted in their files.

3.8 Sponsor sign-off

The Amendment Tool section 3 requires the name and email address of the Sponsor's authorised representative. It should only be completed by the RGM, or delegate. Once this has been authorised the RGT will click on the 'Lock for submission' button which generates a locked PDF copy of the completed Amendment Tool. This shall be returned to the applicant and should be saved to a secure PC.


❗ Unless submitted to RGT for authorisation this will not be an authorised amendment.

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- 3.9 The Amendment Tool categorises the amendment and provides tailored guidance on the submission process. Once the applicant receives the locked PDF from the RGT they should follow the instructions to submit the amendment online via the IRAS online amendment portal (if required). The tool identifies any review bodies which the amendment requires to be sent to; based on the changes that are being made to the study and provides detailed information about sending the amendment to participating sites.


Non-notifiable amendments


- 3.10 The RGT will confirm that your amendment is a non-notifiable amendment. For both single centre and multi-centred projects, non-notifiable amendments do not need to be submitted using the online amendment portal. The locked amendment tool and any corresponding documents should be forwarded to the affected NHS R&D office(s) by email.
-  Non-notifiable amendments do not require REC or R&D approval. They are provided to R&D/ research teams to allow arrangements to be put in place to implement the amendment. The CI/PI should ensure that local procedures are followed for ensuring that NHS R&D Permission is unaffected by the amendment.
- 3.11 The CI, or delegate, must file copies of all correspondence and documents sent to, and from RGT and NHS R&D in the TMF.
- 3.12 The CI must update the TMF with all amended documents and record these in the study specific substantial and non-substantial amendment log (TMP-QA-9).
- 3.13 For multicentre research projects, the responsibility is delegated to the CI to distribute the amendment and related documentation to the PI or other organisations (eg labs, pharmacy etc) as required.

Non-Substantial and Substantial amendments



- 3.14 If the project is single-centred a copy of the amendment shall be submitted online and forwarded to the NHS R&D office(s).
- 3.15 If the project is multi-centred a copy of the amendment shall be submitted online. The central R&D function for the lead nation (usually NRSPCC or HRA) shall receive a copy from the IRAS system and notify other nations if required.
- 3.16 Non-substantial amendments do not need to be approved by the REC or MHRA. NHS R&D shall be notified of all non-substantial amendments as they occur and these shall be categorised as per the **UK Amendment Tool**. The applicant, on completion of the Amendment tool, shall receive notification of the relevant categorisation, who it should be sent to and whether the amendment can be implemented immediately, or if a 35 day implementation date applies. It is the responsibility of the CI (or delegate) to ensure that NHS R&D departments receive amendment documentation.
- 3.17 After the 35 day implementation date an amendment can be implemented if R&D has not raised an objection and all other approvals are in place (where required). As per the UK Amendment Process an R&D Permission letter may not be issued. It is the Sponsor, or delegate's, responsibility to ensure that no amendment is implemented without the required regulatory approvals and either a R&D Permission letter, or after the 35 day implementation date has elapsed.
-  It is best practice to notify the REC and MHRA of any non-substantial amendments, for information purposes, the next time there is communication with the organisation eg next substantial amendment or annual report submission.

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- 3.18 Final copies of all documents, with appropriate version numbers, sent to the MHRA and/or REC shall be sent to the RGM, or delegate, for filing in the Sponsor file, along with copies of submission letters (if required); which should list any enclosed/attached documents.
- 3.19  For amendments to Research Tissue Banks and Research Databases the IRAS Substantial Amendment form shall be submitted online in place of the Amendment Tool.

Reporting of Amendments to the MHRA (CTIMP STUDIES ONLY)

- 3.20  Not all amendments in a CTIMP are required to be reported to the MHRA this will be indicated by the amendment tool or Sponsor.
- 3.21 It is the CI, or delegate's, responsibility to complete and submit the Amendment tool, together with all relevant documents (in the appropriate format).
-  An updated Clinical Trial Application (CTA) form/ Medicines information form (previously called CWOW clinical dataset) shall be submitted if there are any changes to the information originally submitted to the MHRA.



CTIMPs submitted **prior** to the combined review service:

- 3.22 On receipt of the documentation, the MHRA shall acknowledge and validate the submission to the person submitting the application, as defined in section 'C' of the CTA. If the application is invalid, the person making the submission shall be informed of the issue. The application shall not progress until it is valid.



CTIMPs submitted **via** the combined review service:


- 3.23 The amendment should be created and submitted using the new part of IRAS instead of submitting through the IRAS online amendment portal. For guidance on this process follow the guidance outlined on the HRA Combined Review webpage [here](#).

For CTIMP's submitted via either route

- 3.24 Following receipt of a valid amendment, the MHRA will usually review the amendment within a maximum of 35 working days from receipt of the valid submission.
- 3.25 After the amendment has been assessed (within 35 days), the applicant shall be sent a letter stating either:
- Acceptance of the amendment
 - Acceptance of the amendment subject to conditions
 - Grounds for non-acceptance of the amendment
- 3.26 If the CI receives an acceptance of amendment subject to conditions, they shall respond to the MHRA detailing how the conditions shall be met. The MHRA shall send a subsequent letter to the CI approving (or not) the response. Copies of all documentation shall be filed in the TMF and copied to the RGM, or delegate.
-  An amendment must not be implemented until an MHRA approval letter has been received and, if appropriate, REC approval and R&D permission are received.
- 3.27  Should the MHRA send a 'grounds for non-acceptance' email or letter, the CI must **not** implement the amendment. The CI may revise the proposed amendment and make a new application to the MHRA for consideration.

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- 3.28  Where international sites are involved in the clinical trial, the substantial amendment should be submitted to, and approved by, the relevant competent authority and national ethics committee in each country before the amendment is implemented in that country.
- 3.29 If the amendment requires approval from the MHRA only, a copy of the appropriate documents should be forward to the REC which provided the favourable opinion about the trial, for information purposes, the next time there is communication with the organisation eg next substantial amendment, annual report submission etc.




Reporting of Amendments to the REC (ALL RESEARCH STUDIES)

- 3.30 On receipt of the documentation, REC shall confirm to the CI within five working days whether the application is valid or not. REC (under normal circumstances) shall issue an opinion on the amendment within a maximum of 35 working days from receipt of a valid Amendment tool.



Modified amendments


- 3.31 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, indicating that it relates to a modified amendment at the relevant question. It should then be submitted to the REC alongside all supporting documentation by email. Modified amendments must not be submitted using the online portal. REC email addresses can be looked up on the [HRA website](#).
-  If the REC does not give a favourable opinion, the CI may appeal within 90 days of being notified of the unfavourable opinion.
- 3.32 If the amendment requires approval from the REC only, a copy of the appropriate documents shall be forwarded to the MHRA, for information purposes, the next time there is communication with the organisation eg next substantial amendment, annual report submission etc.

Implementing an Amendment







- 3.33 The amendment shall only be implemented once all necessary approvals have been received.
- 3.34 For an amendment requiring approval from the REC alone or the MHRA alone (CTIMPs only), the CI may implement the amendment once the REC has provided a favourable opinion or the MHRA has not raised grounds for non-acceptance of the amendment (respectively). Where R&D approval is required, either a letter confirming continuing permission for the amendment should be received from R&D, or the 35 day implementation date must have passed, after which an amendment can be implemented if no objection has been received.
- 3.35 The CI, or delegate, must make any changes to the amended documents as requested by the REC and/or MHRA, and resubmit the documents as necessary.
- 3.36  The CI, or delegate, must send copies of **all** further correspondence and documents sent to and received from the MHRA and/or REC to the RGT, and NHS R&D office (if single-centred), or NRSPCC (if multi-centred).
- 3.37  The CI, or delegate, must file copies of all correspondence and documents sent (including copies of signed cover letters) to, and from, the REC and/or MHRA and NHS R&D in the TMF.
- 3.38  The CI, or delegate, must log all amendments in a trial specific substantial and non-substantial amendment log (TMP-QA-9).

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- 3.39  It is the responsibility of the CI to notify any other relevant individuals (eg Principal Investigators (PIs) if a multisite research project) or organisations (eg drug supply company, labs, pharmacy etc) that all necessary approvals have been received before an amendment can be implemented.

Procedure after REC approval, R&D Permission (and/or MHRA approval if required)

- 3.40  The CI must provide the Sponsor with a copy of any documentation amended as a result of correspondence with the REC, R&D (and/or MHRA).
- 3.41  The CI must update the TMF with all amended documents and record these in the study specific substantial and non-substantial amendment log (TMP-QA-9).
- 3.42  The CI/PI must ensure that the amendment approval letters from the REC, R&D (or notification of implementation date) (and/or the MHRA) are filed in the appropriate sections of the TMF and/or Investigator Site File/Investigator TMF.
- 3.43  For multicentre research projects, the responsibility is delegated to the CI to ensure all sites involved are able to support the amendment, and to distribute the amendment and related documentation to the PI or other organisations (eg drug supply company, labs, pharmacy etc) as required.
- 3.44  The CI shall discuss with Sponsor any problems that centres might have in supporting the amendment. Such centres may be unable to continue their involvement with the project.
- 3.45  The CI/PI must ensure that all staff involved in the research project are aware of any amendments, and that they comply with the amendments. It is also the CI/PI's responsibility to inform the local pharmacy of any amendments to the research project if a CTIMP.
- 3.46 The CI/PI should ensure that local procedures are followed for ensuring that NHS R&D Permission is unaffected by the amendment.

4. Abbreviations and definitions

CI	Chief Investigator
CSOG	Clinical Studies Oversight Group
CTA	Clinical Trial Application
CTIMP	Clinical Trial of Investigational Medicinal Product
MDCI	Medical Device Clinical Investigations
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research and Development (NHS)
REC	Research Ethics Committee
RGM	Research Governance Manager
RGT	Research Governance Team
TMF	Trial Master File

5. Related documentation and references

SOP-QA-10	Applying for Research Ethics Committee opinion
SOP-19 Appendix 1	Examples of substantial and non-substantial amendments
TMP-QA-9	Amendments log

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Appendix 1: Examples of Substantial, Non-substantial and Non-Notifiable Amendments

All amendments must first be reviewed and approved by Sponsor.

Substantial Amendments (Details should be forwarded to R&D departments if single centre)

Substantial Amendment	REC	MHRA*
Changes to the design or methodology of the study, or to background information affecting its scientific value eg use of new measurement for the primary end point, addition of trial arm, placebo group	N	N
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 eg change of inclusion/exclusion criteria, reducing monitoring visits, withdrawal of an independent data monitoring committee	N	N
Significant changes to study documentation eg participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers	N	I
A change of Sponsor(s) or Sponsor's legal representative	N	N
Appointment of a new Chief Investigator or key collaborator	N	I
A change to the insurance or indemnity arrangements for the study	N	I
Temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt	N	N
A change to the definition of the end of the study	N	N
Any other significant change to the protocol or the terms of the REC application	N	N
Suspension or revocation of the IMP marketing authorisation	N	N
Change of IMPs used, dosing regimen, mode of administration	N	N

Non-substantial Amendment (Details should be forwarded to R&D departments if single centre)

Non-Substantial Amendment	REC	MHRA*
Minor changes to the protocol or other study documentation, eg correcting errors, updating contact points, minor clarifications	I	I
Updates of the Investigator's Brochure (unless there is a change to the risk/benefit assessment for the trial)	I	I
Changes in funding arrangements	I	I
Changes in the documentation used by the research team for recording study data;	I	I
Changes in the logistical arrangements for storing or transporting samples	I	I
Inclusion of new sites and investigators in all studies	I	I
Extension of the study beyond the period specified in the application form	I	I

Non-notifiable Amendment (Details should be forwarded to R&D departments)

Non-Notifiable Amendment	REC	MHRA*
Changes to the Chief Investigator's research team (other than appointment of key collaborators)	I	I
GDPR wording- accepted wording used verbatim	I	I
Addition of translated versions of participating documents	I	I

Key

*— CTIMP only

N – Notify body of the amendment by sending all documentation required. Wait for approval before implementing

I – Send a copy all correspondence regarding the amendment for information only when next submitting a substantial amendment or annual report.

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