SOP-QA-19 V7

Title: Modifications

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Document History

Version	Description of update	Date Effective
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	09-7-23
7	New author Updated reference from amendments to modifications (including title) and revised process throughout	28-04-26

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 modifications to the protocol, essential documentation or other aspect of a study's arrangements.

⚠ This SOP does not cover modifications 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 modification 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 modifications from Sponsor, ensure all documents are subject to version control and are filed in the Trial Master File (TMF).
Research Governance	Review and classify modifications, ensure that insurance is still in place after any modification and review and update the risk assessment (as required).

3. Procedure

Classification of Modifications

3.1 Modifications are classified as substantial, modification of an important detail, minor or non-notifiable.

3.2 **Substantial** modifications are considered to be a modification to a study 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 CTIMPs, substantial modifications are further classified as Route A or Route B, and the MHRA will process a substantial modification differently depending on whether it is Route A or B. Full details on Route A and B modifications can be found on the MHRA website.

3.3 **A modification of an important detail** is defined as a change to the details of the study that do not significantly impact the safety or rights of the participants, which the MHRA (CTIMP) and REC only need to be made aware of for administrative or oversight purposes. These types of modification are not reviewed by the REC or MHRA (CTIMP) and no outcome will be issued. They are for information only. These modifications may however need other approvals (for example R&D, HRA and HCRW approval).

3.4 Minor modifications are changes that do not fall into the category of 'substantial modification' or 'modification of an important detail'. These do not require REC or MHRA (CTIMPs) approval but may require other approvals (for example R&D, HRA and HCRW approval)

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

Examples of substantial modifications, modification of an important detail, and minor modifications are available on the HRA website. .

Requesting Authorisation of Modifications 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 a modification.

3.6 All modifications for research projects (with the exception of tissue bank and research databases) shall use the IRAS Modification Tool. The modification 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 modified documents to the RGT. The RGT shall review the modification documentation and discuss and agree the modification with the CI, or delegate, as necessary. Whilst reviewing any modification the RGM, or delegate, shall consider if it alters the risk of the study. Any modification 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 modifications 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 a modification moves it into the referral criteria) subsequent substantial modifications 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 modification 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 modification 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 modification.

3.9 The modification tool categorises the modification 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 modification online via the IRAS online modification portal (if required). CTIMPs (prior to combined review) should submit via the IRAS modification portal and to the MHRA via MHRA submissions. CTIMPs submitted via combined review should **not** submit via the IRAS online modification portal but instead should submit through IRAS combined review system. The tool identifies any review bodies which the modification requires to be sent to; based on the changes that are being made to the study and provides detailed information about sending the modification to participating locations/sites.

Non-notifiable modification

3.10 The RGT will confirm that the modification is non-notifiable. For both single centre and multi-centred projects, non-notifiable modifications do not need to be submitted using the online portal. The locked tool and any corresponding documents should be forwarded to the affected NHS R&D office(s) by email.

Non-notifiable modifications 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 modification. The CI/PI should ensure that local procedures are followed for ensuring that NHS R&D Permission is unaffected by the modification.

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 modification log (TMP-QA-9).

3.13 For multicentre research projects, the responsibility is delegated to the CI to distribute the modification and related documentation to the PI or other organisations (eg labs, pharmacy etc) as required.

Minor, modification of an important detail and substantial modifications

3.14 If the project is single-centred a copy of the modification 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 modification 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 Minor modifications do not need to be approved by the REC or MHRA. NHS R&D shall be notified of all minor modifications as they occur. The modification tool will classify whether the modification 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 modification documentation.

3.17 After the 35 day implementation date a modification can be implemented if R&D has not raised an objection and all other approvals are in place (where required). As per the UK Modification Process an R&D Permission letter may not be issued. It is the Sponsor, or delegate's, responsibility to ensure that no modification is implemented without the required regulatory approvals and either a R&D Permission letter, or after the 35 day implementation date has elapsed.

3.18 Final copies of all documents, with appropriate version numbers, submitted as part of a modification 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 modifications to Research Tissue Banks and Research Databases the IRAS Substantial Modification form shall be submitted online in place of the Modification Tool.

Reporting of modification of an important detail (CTIMP studies only)

3.20 Instructions for notifying the authorities (REC and MHRA) about a modification of an important detail are provided on completion of the modification tool.

Reporting of Substantial Modifications to the MHRA (CTIMP STUDIES ONLY)

3.21 Not all modifications in a CTIMP are required to be reported to the MHRA this will be indicated by the tool or Sponsor.

3.22 It is the CI, or delegate's, responsibility to complete and submit the tool, together with all relevant documents (in the appropriate format).

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

3.23 The modification tool and associated documents should be submitted online via the IRAS modification portal and, where considered a substantial modification, via MHRA submissions.

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

3.24 The modification should be created and submitted using the new part of IRAS instead of submitting through the IRAS online portal. For guidance on this process follow the guidance outlined on the HRA Combined Review webpage here.

For CTIMP's submitted via either route

3.25 On receipt of the documentation, the MHRA shall acknowledge and validate the submission within 7 calendar days. As soon as possible during this period and no later than the fifth calendar day the MHRA may notify the applicant by email of any deficiencies identified and allow them to be addressed. These must be addressed by the end of the 7-day period otherwise the application will be invalidated and will need to be resubmitted with the deficiencies corrected. The application shall not progress until it is valid.

Route A substantial modifications

3.26 Route A modification, upon receipt of a valid modification, the MHRA and/or REC will usually review it within a maximum of 35 working days from receipt of the valid submission.

3.27 After the modification has been assessed (within 35 days), the applicant shall be sent a letter stating either:

- the authorities approve the proposed modification
- the authorities approve the proposed modification subject to conditions

- the authorities do not approve the proposed modification, setting out the grounds for this decision

3.28 If the authorities approve the proposed modification subject to conditions the modification is considered approved all of the conditions are satisfied. The Sponsor should keep record of how the conditions have been met but it is not necessary to inform the authorities that the condition has been met before implementing the modification unless otherwise stated in the approvals letter. Copies of all documentation shall be filed in the TMF and copied to the RGM, or delegate.

A modification must not be implemented until an authorities approval letter (with or without conditions) has been received and any conditions have been resolved and documents and R&D permission are received.

3.29 Should the authorities not approve the proposed modification email or letter, the CI must **not** implement the modification. The CI will be given one opportunity to provide further information (60 days) and have the application re-considered. If this deadline is not met this will be rejected. If the application is still not approved, the reasons will be outlined and this will be treated as rejected. No further changes to that modification will be considered however the applicant may submit a new proposed modification and make a new application to the authorities for consideration.

Route B substantial modifications

3.30 All Route B substantial modifications should be detailed as such in the covering letter to the MHRA. Once this is confirmed as valid the applicant will receive confirmation by email that the Route B substantial modification has been received by the MHRA.

3.31 For Route B substantial modifications, these will receive automatic approval from the MHRA. If the application meets the eligibility criteria for a Route B substantial modification confirmation of automatic approval from the MHRA will be issued by email within 14 calendar days of validation. Where no REC opinion is needed, the notice of automatic approval will specify that this represents a joint decision from the MHRA and REC.

3.32 If REC approval is also required for the Route B substantial modification this will be processed by the REC in the same way as Route A substantial modifications and the initial combined decision on approval of the Route B substantial modification will be issued within 35 calendar days of validation.

3.33 The modification cannot be implemented unless a combined decision that the modification is approved (or approved with conditions) is received.

3.34 If the MHRA finds that an application does not meet the eligibility criteria the applicant will be issued a letter stating this, and the reason for objection, via email within 14 calendar days of validation. The application will then automatically undergo review as a Route A substantial modification, unless the applicant chooses to withdraw the application, with a combined decision within 35 days.

3.35 Where international sites are involved in the clinical trial, the substantial modification should be submitted to, and approved by, the relevant competent authority and national ethics committee in each country before implementation in that country.

Reporting of Modifications to the REC (NON-CTIMPs)

3.36 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 modification within a maximum of 35 working days from receipt of a valid tool.

Revised Modifications (NON-CTIMPs)

3.37 Where the REC gives an unfavourable opinion of a substantial modification, the sponsor or CI may submit a revised modification, taking account of the Committee's concerns. In this case a new tool should be completed, indicating that it relates to a revised modification at the relevant question. It should then be submitted to the REC alongside all supporting documentation by email. Revised modifications 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 28 days of being notified of the unfavourable opinion.

Implementing a Modification (ALL RESEARCH STUDIES)

3.33 The CI, or delegate, must make any changes to the modified documents as requested by the REC and/or MHRA, and resubmit the documents as necessary.

3.24 The modification shall only be implemented once all necessary approvals have been received.

3.35 For a modification requiring approval from the REC alone or the MHRA alone (CTIMPs only), the CI may implement once the REC has provided a favourable opinion or the MHRA has not approved the modification (respectively). Where R&D approval is required, either a letter confirming continuing permission for the modification should be received from R&D, or the 35 day implementation date must have passed, after which a modification can be implemented if no objection has been received.

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 modifications in a trial specific modification log (TMP-QA-9).

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 modification 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.

3.43 It is the responsibility of the CI to ensure all locations/sites involved are able to support the modification, and to distribute the modification and related documentation to the PI(s) or other organisations (eg drug supply company, labs etc) as required. In a CTIMP it is also the CI/PI's responsibility to inform the local pharmacy of any modifications to the research project before a modification can be implemented.

3.44 The CI shall discuss with Sponsor any problems that locations/sites might have in supporting the modification. Such locations/sites may be unable to continue their involvement with the project.

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
TMP-QA-9	Modifications log