

Joint Research Management Office Standard Operating Procedure for:

Modifications for sponsored studies (including halting studies) - Process for researchers

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Purpose:

To ensure that the Coordinating Investigator (CI), or delegate, is aware of the procedure for seeking approval for modifications on studies sponsored by Barts Health NHS Trust (Barts Health) and Queen Mary University of London (Queen Mary).

To ensure that the CI, or delegate, receives approval from the Joint Research Management Office (JRMO) for all sponsored modifications prior to submission to the research ethics committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA) or Health Research Authority (HRA) prior to implementation, as applicable.

To ensure that location authorisation is received (as per local location procedure) before the modification is implemented at any research location.

To ensure that the current approved versions of documents are contained in the trial master file and location investigator files at every research location.

Scope:

This standard operating procedure (SOP) applies to all studies sponsored by Barts Health and Queen Mary. However, the process of obtaining approvals from the REC, MHRA and HRA is written in the context of England and will vary in devolved administrations and other countries.

For externally sponsored studies hosted at Barts Health, please refer to [SOP 17b: Modifications for hosted studies](#).

For JRMO internal processes please refer to [SOP 17a: Modifications for sponsored studies \(including halting studies and early termination\) - Process for JRMO](#)

Abbreviations:

Barts Health	Barts Health NHS Trust
CAG	Confidentiality Advisory Group
CI	Coordinating Investigator
EoT	End of Trial
HRA	Health Research Authority
JRMO	Joint Research Management Office

MHRA	Medicines and Healthcare products Regulatory Agency
Queen Mary	Queen Mary University of London
REC	Research Ethics Committee
SOP	Standard Operating Procedure

SOP Text:

	Responsibility	Activity
1.	CI	Prepare the modification submission and ensure that the modification has been reviewed scientifically and statistically. - Consider the impact upon participant safety, support departments (i.e., imaging/pharmacy/clinical physics), training, study specific SOPs, risk assessment and Case Report Forms. - Where the modification affects the study protocol, key study documents or eSystems, consider if a full review of the risk assessment is required. - Ensure that there is sufficient funding to cover any additional study costs that will be incurred due to the modification, complete the <u>JRMO confirmation of cost for modifications form (Associated Document 1)</u> and liaise with the JRMO costing team where necessary. - Seek JRMO contract & costing approval if the modification affects additional resources or contracts, receipt of additional services/goods/equipment, change or addition of contracts, use of new vendors/suppliers or central facilities. - Where a modification is adding a new vendor, potential vendor assessment may be required. See <u>SOP 40 Vendor Assessment</u> for further details. - Complete the HRA Modification Tool correctly which can be found via <u>https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool</u> or the modification form available in IRAS for research tissue banks/research databases. - Update the study documents (including version & date) as tracked changes. Ensure that all required documents are updated - for example if the protocol has changed then the Patient Information Sheet and/or GP letter may also need to be updated. - Obtain peer review of scientific aspects of the modification such as changes to the design of the protocol, as applicable. - The study statistician where applicable, (as named on the protocol/IRAS form) must approve all modifications that affect patient numbers, randomisation, study design or have any other statistical implications. - Obtain approval from relevant support departments and individuals as required: - Information Governance - Imaging/Radiation (all scans) - Medical Physics (all changes to equipment and devices)

		○ Pathology (changes to storage or lab analysis) ○ Pharmacy (changes to the Investigational Medicinal Product or associated documents) ○ Host locations: establish if the proposed modification is feasible at all locations ○ eSystems Manager/Database Developer: Additions of new eSystems or updates to current eSystems must be supported by new/updated validation documentation. Any new/updated eSystem must not go live until full modification review and approval has been completed.
2.	CI	Submit the modification to the JRMO for approval. Send a valid modification submission (see below) to the JRMO via research.amendments@qmul.ac.uk. In corresponding with the JRMO, specify the study IRAS ID number. The email should state whether the CI considers the Modification to be substantial, a modification of an important detail, or a minor modification, but the JRMO will determine the final classification of the modification. A valid modification submission consists of: • HRA modification tool/ Modification form (for research tissue banks/ research databases). • CAG modification form (for studies that have Confidentiality Advisory Group (CAG) approval and if the modification itself changes any CAG aspects from the original CAG approval) • All new or modified documents. Modified documents should be submitted in both 'clean' and 'tracked changes' versions. Revised protocols must be signed by the CI (and statistician for MHRA-regulated studies). • Signed Confirmation of Costs for Modifications (Associated document 1) – required for all modifications. • Signed conditions of sponsorship (if a new CI is appointed). • Modification log (Complete Modification log for every modification when you are submitting to JRMO and if it is a substantial modification, include all prior minor modification references that have not already previously been communicated to regulators in the cover letter accompanying each new Substantial Amendment submission. The cover letter also needs to include a statement explaining why the applicant considers the modification to be a Route B substantial modification. • MHRA regulated studies only please use this link for guidance on the different modification types and routes. Clinical trials for medicines: modifying a clinical trial approval - GOV.UK • Modification of important detail – does not affect patient safety or rights and is submitted as notification only to reg bodies. • Substantial modifications Route A - affects scientific value and patient safety submitted to regs as normal • Substantial modifications Route B – no safety concerns to patients due to modification, no safety concerns with any IMP involved. These are still submitted to ethics as normal. Only considered route B if one of the A B C conditions below are met. Condition A: The trial does not involve a first-in-human investigational product, and the modification has been approved by a recognised authority (EU, EEA, or USA).

		Condition B: limited to a specific set of changes to the trial protocol (e.g. study design, objectives, measurements). Condition C: limited to a specific set of changes to the investigator's brochure or summary product characteristics (e.g. safety updates, adverse event frequencies). If any of the above are involved, then it is no longer route B but instead route A. • Minor modifications – are not submitted to review bodies they are just logged in TMF each time this happens in a study by CI/research team and can be implemented straight away once JRMO has reviewed and locked the tool. When research teams submit a substantial modification, a list of all minor modifications that have happened are to be included for info via cover letter to reg bodies. If the Modification is to be submitted to the MHRA, supporting data may be required, as applicable. For example, summaries of data, updated risk benefit assessment, possible consequences for participants on the study and possible consequences for evaluation of results. For CI/local Investigators on long term leave (3+ months), a modification to temporarily replace the CI/Investigator or halting the study should be submitted.
3.	CI	Submit to the regulators once you have JRMO approval. The JRMO will review the modification and provide feedback. Once all feedback has been addressed, the JRMO will approve the modification by authorising/locking the HRA modification tool or modification form. All Substantial modifications must be submitted as per modification tool outcome. Some substantial modifications for MHRA-regulated studies must also be submitted to the MHRA. Gaining regulatory (REC, HRA, MHRA, CAG) approval: Submit the locked modification tool and supporting documents reviewed by sponsor (clean and tracked) via the IRAS portal (non-MHRA regulated) or the combined review IRAS portal (MHRA regulated). For modifications that also require CAG approval, submit the CAG modification form and any relevant updated documents via email to cag@hra.nhs.uk and copy in allocated RMGO that reviewed the modification. Once the Modification has been signed off by the JRMO, if it is Minor Modifications, it can be implemented straight away, otherwise submit to the regulators for approval. A list of all minor modifications that have happened and have not previously been notified to ethics via a substantial modification, should be detailed within a cover letter to be submitted at the next Substantial modification.
4.	CI	If the REC, MHRA, CAG or HRA request further changes to the modification, seek JRMO sponsor approval before replying to them. If after submission of the modification, the regulatory bodies request changes to documents, the revised documents must be reviewed by Governance/Good Clinical Practice team, as applicable. After you have the regulatory approvals, you will need to wait for final sponsor approval to implement Forward all correspondence to and from the REC, MHRA, CAG and HRA, and additional documents to the JRMO in a timely manner.
5.	CI	Distribution of modification package to the locations.

		The CI should send the modification package and categorisation email to the following teams within the participating NHS organisations: • Study Delivery Team • R&D Office Locations can then begin to assess continued Capacity and Capability of the modification while waiting for review body approval.
6.	CI	Submit the approved document set to the JRMO. • Once REC, MHRA, CAG and/or HRA approvals are in place, forward the approved documents to research.amendments@gmul.ac.uk. • A valid approved modification is: ○ Final fully signed modification tool/ modification form. ○ REC, CAG and MHRA approval letters (where applicable) and all correspondence. ○ HRA approval of the modification and all correspondence (where applicable) (Note: Where REC Approval is also required, continuing HRA Approval is conditional on Favourable REC Opinion). ○ All modified documents as listed on REC approval letter (if modification was substantial and received REC Approval). ○ Revised protocol signed by the CI (and statistician for MHRA-regulated studies) if changes were required.
7.		Implement modification at locations. It is the responsibility of the investigative team to comply with any further local review processes prior to implementing the amendment.
Special modifications		
8.		Implement urgent safety measures (USM) immediately, seek advice from the HRA, MHRA and sponsor before (if possible), and inform the MHRA & REC in writing by submitting a substantial modification within 7 days. The sponsor and investigator may implement urgent safety measures to protect clinical trial participants from immediate hazards to their health and safety. This is the only time that a modification can be made to a study without first obtaining review body approval. Where possible, the CI should discuss the urgent safety measure with the sponsor and MHRA Clinical Trials Helpline before implementing the modification. Once an urgent safety measure has been implemented, the CI must notify the MHRA and REC in writing in the form of a substantial modification within seven days. For further details please see JRMO SOP 26a Location level Pharmacovigilance for MHRA regulated studies.
9.		When a study is 'halted' inform the regulators and JRMO. If the sponsor or CI decides to formally halt the study temporarily, it is the CI's responsibility to notify the REC (and MHRA for MHRA-regulated studies) immediately and at the latest within 15-days from when the study is temporarily halted.

		A temporary halt is defined as a stoppage of either the study, or one or more research location not foreseen in the protocol, but with the intent to resume the trial in the future. The notification will be made as a modification by the CI and must clearly explain what has been halted (for example, stopping recruitment and/or interrupting treatment of participants already included) and the reasons for the temporary halt. To restart a study that has been temporarily halted, the CI must immediately provide evidence that it is safe to restart the study and submit a modification to restart. Keep written copies of correspondence to REC and MHRA halting the study and send copies of all correspondence and documents to the JRMO.
10		When a study stops early, submit a notification of early termination to the JRMO and review bodies. Where a study is terminated early (i.e., before the end of trial definition has been reached as defined in the protocol), the End of Trial (EoT) Form must be submitted to the MHRA and REC within 15 days. For full guidance see SOP 18a Study closure for sponsored studies. Once a EoT has been submitted, further modifications cannot be made.

Change control

This section outlines changes from version **5.0** to version **6.0**

Section changed	Summary and description of changes
Throughout	General Administrative changes
Throughout	Update to terminology in line with ICH E6 R3
Throughout	Update to process for modification classification in line with ICH E6 R3

List of associated documents

Document ref.	Document name
Associated document 1	Confirmation of costs form for modifications