Joint Research Management Office Standard Operating Procedure for:

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

SOP Number:	**17c**	Version Number:	**5.0**
Effective Date:	**2nd January 2025**	Review Date:	**2nd January 2028**

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Purpose:

To ensure that the Chief Investigator (CI), or delegate, is aware of the procedure for seeking approval for amendments 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 amendments prior to submission to the research ethics committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA) or Health Research Authority (HRA) and again prior to implementation, as applicable.

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

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

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: Amendments for hosted studies.

For JRMO internal processes please refer to SOP 17a: Amendments for sponsored studies (including halting studies and early termination) - Process for JRMO

Abbreviations:

Barts Health	Barts Health NHS Trust
CI	Chief 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 amendment submission and ensure that the amendment has been reviewed scientifically and statistically.**
		
		• Consider the impact upon patient safety, support departments (i.e., imaging/pharmacy/clinical physics), training, study specific SOPs, risk assessment and Case Report Forms.
		
		• Where the substantial amendment affects the study protocol, key study documents or eSystems, consider if a full review of the risk assessment is required. The decision to reassess risk or not should be documented clearly in the EDGE workflow.
		
		• Ensure that there is sufficient funding to cover any additional study costs that will be incurred due to the amendment, complete the JRMO confirmation of cost for amendments form (Associated Document 1) and liaise with the JRMO costing team where necessary.
		
		• Seek JRMO contract & costing approval if the amendment 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 an amendment is adding a new vendor, potential vendor assessment may be required. See SOP 40 Vendor Assessment for further details.
		
		• Complete the HRA Amendment Tool correctly which can be found via https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool or the Notice of Substantial Amendment form available in IRAS for tissue banks/research eSystems.
		
		• 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 amendment 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 amendments 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 sites: establish if the proposed amendment is feasible at all sites ○ eSystems Manager: Additions of new eSystems or updates to current eSystems must be supported by new/updated validation documentation as per SOP 38b Electronic data management systems for MHRA-regulated studies. Any new/updated eSystem must not go live until full amendment review and approval has been completed.
2.	CI	**Submit the amendment to the JRMO for approval.** Send a valid amendment 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 amendment to be a non-substantial or substantial, but the JRMO will determine the final classification of the amendment. It is possible that an amendment will be substantial to the REC but not to the MHRA (and vice versa). If this is the case the amendment should be treated as non-substantial to the other body. A valid amendment submission consists of: • HRA Amendment tool/ Notice of Substantial Amendment form. • All new or amended documents. Amended 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 Amendments (Associated document 1) – required if the amendment will have any impact on study costs. • Written confirmation from the CI (and statistician if applicable) that they approve all amended documents (if the CI and/or statistician are not copied into the submission email). • Signed conditions of sponsorship (if a new CI is appointed). If the substantial amendment 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 subjects on the study and possible consequences for evaluation of results. For CI/Principal Investigator's (PI) on long term leave (3+ months), an amendment to temporarily replace the CI/PI or halting the study should be submitted.
3.	CI	**Submit to the regulators once you have JRMO approval.** The JRMO will review the amendment and provide feedback. Once all feedback has been addressed, the JRMO will approve the amendment by authorising/locking the HRA Amendment tool or Notice of Substantial Amendment form. All amendments must be submitted via online submission to the REC, who will forward the amendment to the HRA for their review. Some substantial amendments for MHRA-regulated studies must also be submitted to the MHRA.

		Gaining regulatory (REC, HRA, MHRA) approval: Submit the locked amendment tool/ Notice of Substantial Amendment form 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 substantial; category A, B, C and non-substantial notifiable; category A, B, C** Once the amendment has been signed off by the JRMO, it can be submitted to the regulators for approval. **For non-substantial non-notifiable; category C** For this amendment type, the JRMO will sign off the amendment tool so it can be submitted to the regulators for approval. They will also issue approval to implement the amendment. Ensure to forward the HRA notification to sponsor.
4.	CI	**If the REC, MHRA or HRA request further changes to the amendment, seek JRMO sponsorship approval before replying to them.** If after submission of amendment, 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 and HRA, and additional documents to the JRMO in a timely manner.
5.	CI	**Distribution of amendment package to the sites.** The CI should send the amendment package and categorisation email to the following teams within the participating NHS organisations: • Study Delivery Team • R&D Office Sites can then begin to assess continued Capacity and Capability of the amendment while waiting for review body approval.
6.	CI	**Submit the approved document set to the JRMO.** • Once REC, MHRA and/or HRA approvals are in place, forward the approved documents to research.amendments@qmul.ac.uk. • A valid approved amendment is: o Final fully signed amendment form/ Notice of Substantial Amendment form. o REC and MHRA approval letters (where applicable) and all correspondence. o HRA approval of amendment and all correspondence (Where applicable) (Note: Where REC Approval is also required, continuing HRA Approval is conditional on Favourable REC Opinion). o All amended documents as listed on approval letters. o Written evidence that the CI approves the finalised amendment (if changes were required).

		○ Revised protocol signed by the CI (and statistician for MHRA-regulated studies) if changes were required.
7.		**Implement amendments at sites.** Category A or B (requires consideration by site) - Amendments can be implemented 35 calendar days after CI provides the amendment package to the relevant sites, unless concerns/objections are raised (conditional on regulatory approval being in place) by the R&D office. Category C (does not require consideration by site) - Amendments can be implemented immediately after the sponsor provides it to the relevant site unless concerns or objection are raised (conditional on regulatory approval). It is the responsibility of the investigative team to comply with any further local review processes prior to implementing the amendment.
Special Amendments		
8.		**Implement urgent safety measures immediately, seek advice from the HRA, MHRA and sponsor before (if possible), inform the MHRA & REC within 3-days and submit an amendment within 2 weeks.** 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 an amendment 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 amendment. Once an urgent safety measure has been implemented, the CI must notify the MHRA and REC in writing within three days. The CI must also prepare a retrospective substantial amendment to document the urgent safety measure. This should be submitted to the review bodies within two weeks of the urgent safety measure. For further details please see JRMO SOP 26a Site 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 sites not foreseen in the protocol, but with the intent to resume the trial in the future. This includes studies where the stoppage was not envisaged in the approved protocol. The notification will be made as a substantial amendment by the CI and must clearly explain what has been halted (for example, stopping recruitment and/or interrupting treatment of subjects 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 substantial amendment 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 amendments cannot be made.

Change control

This section outlines changes from version **4.0** to version **5.0**

Section changed	Summary and description of changes
Throughout	General administrative changes
Throughout	Inclusion of consideration to e-system changes
Section 1	Consideration to update risk assessment

List of associated documents

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