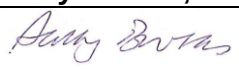
Standard Operating Procedures (SOP) for:			
Process for Researchers - Amendments for Sponsored Studies (including halting studies and early termination)			
SOP Number:	**17c**	Version Number:	**2.0**
Effective Date:	**19/9/16**	Review Date:	**19/10/17**

Author:	**Elizabeth Clough, R&D Governance Operations Manager**
Reviewer :	**Safia Ornelas, Research Management and Governance Officer**
Reviewer :	**Marie Claire Good, GCP and Governance manager**

Authorisation:	
Name / Position	**Sally Burtles, Director of Research Services & Business Development**
Signature	
Date	**25/8/16**

Purpose and Objective:
To ensure that the Chief Investigator's (CI), or delegate is aware of the procedure for seeking approval for amendments on projects sponsored by Barts Health NHS Trust (BH) and Queen Mary University of London (QMUL). To ensure that the CI, or delegate, receives JRMO approval as sponsor for all sponsored amendments prior to submission to REC, HRA or MHRA. To ensure that Site authorisation is received 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 (TMF) and Site Investigator Files (ISF) at every research site.
Scope:
This SOP applies to all projects sponsored by Barts Health NHS Trust and Queen Mary University London. For BH/QMUL as a site please refer to SOP 17b: Amendments for Hosted Studies. For JRMO internal processes please refer to SOP 17a: JRMO Process - Project Amendments for Sponsored Studies (including halting studies and early termination)

Abbreviations:	
BH	Barts Health NHS Trust
JRMO	Joint Research Management Office
HRA	Health Research Authority
NHS	National Health Service
QMUL	Queen Mary University of London
T&Cs	Terms and Conditions
TMF	Trial Master File
LCRN	Local Clinical Research Networks
PI	Principal Investigator
CI	Chief Investigator
TMF	Trial Master File
NOSA	Notification of Substantial Amendment
REC	Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
IRAS	Integrated Research Application System
CTIMP	Clinical Trial of an Investigational Medicinal Product
CESP	Common European Submission Portal
ISF	Investigator Site File

Relevant SOPs
SOP 17b Amendments for Hosted Studies. SOP 17a Process for JRMO - Amendments for Sponsored Studies

SOP Text

	Responsibility	Activity
1.	Chief Investigator	**Ensure that the amendment has been reviewed scientifically, statistically (if required) and consider the impact upon patient safety, the budget and NHS costs including support departments (imaging/pharmacy/clinical physics, if any).** • Ensure that there is sufficient funding to cover any additional study costs that will be incurred, due to the amendment, completing the JRMO cost form and liaising with JRMO costing team where necessary. • Seek JRMO Contract & Costing approval if changes affect additional resources, receipt of additional services/goods/equipment, change or addition of contracts, use of new vendors/suppliers or central facilities. • Complete the amendment form in IRAS (see IRAS for guidance) • Update the study documents (including version & date) in track-changes. • Where there are substantial changes to the study design, liaise with any support departments regarding the feasibility of the proposed amendment. • Study Statistician (as named on the protocol/IRAS form) must approve all amendments that affect patient numbers, randomisation or study design. • Imaging and pharmacy approval must be sought if any changes are made to imaging or IMP. • Additional applicable should be sought if applicable: - Information Governance - Imaging/Radiation (all scans) - Medical Physics (all changes to equipment and devices) - Tissue (changes to storage or lab analysis) - Multisite studies: establish if the proposed amendment is feasible at all sites - Changes to databases (i.e. changing to a new database) • Where applicable update the Clinical Trial Authorisation Form (QMUL or BH Sponsored CTIMP) Send a valid amendment submission (see below) to JRMO. In corresponding with the JRMO, detail the project ReDA number and state scope e.g. non-substantial Amendment for sponsored study. The email should state whether the CI considers the amendment to be minor or substantial. The decision whether an amendment is substantial or non-substantial is made by the Sponsor. It is possible that an amendment will be substantial to one of REC or MHRA but not the other. If this is the case the amendment should be treated as minor to the other body. • A valid amendment submission consists of: - IRAS Amendments Form (for all CTIMPs both the authorisation and D.1.1 D.2.1 are signed by the Sponsor and not the CI). - Cover Letter to REC. - Cover Letter to the MHRA (if applicable). - All amended documents with track changes. - Completed and signed Cost Declaration Form. - Plus any supporting department approvals already secured by the CI, e.g. pharmacy approval. - Written evidence (email) that the CI approves the amendment. - Revised protocols must be signed by the CI (CTIMPs only: and Statistician).

		Consideration for substantial amendments to MHRA:
		- Proof of payment of fee - see guidance on the MHRA website on making a payment. Ensure evidence of payment is included in MHRA application and sent to JRMO.
		- The MHRA application should make clear the reasons for the proposed changes to the protocol or other document (e.g. investigational medicinal product dossier), and show previous and new wording in track-changes.
		- Supporting information for the proposed change, including:
		  - Summaries of supporting information
		  - Updated overall risk-benefit assessment, considering possible consequences for subjects already in the trial.
		  - Possible consequences for the evaluation of results
		For more information on the types of documents that can be submitted to avoid issues with an application - state the EudraCT number, which is used as a reference number. Await written approval from the JRMO amendment team.

2.	Chief Investigator	**Submit to REC and MHRA once you have sponsor approval**
		
		Substantial Amendments
		Upon receipt of written Sponsorship approval for the amendment via an email from the JRMO, submit all amendment documents to the MHRA and or REC (as applicable) and cover letter.
		
		• **Gaining REC approval:** On the IRAS form ensure that REC has been ticked'.
		- Submit to REC by email (see HRA website for further details). Information will be automatically shared internally with the HRA Assessment Team. This is the same for studies that were set-up using the pre-HRA Approval processes and those that were approved by the HRA.
		- Submit the complete Notification of Substantial Amendment form (NOSA).
		- Submit the latest version of the docs to REC.
		- If the REC is in Northern Ireland, Scotland or Wales, please copy in hra.amendments@nhs.net
		
		• **Gaining HRA approval**
		- REC will share documents with HRA.
		- HRA categorise the amendment in 5 working days (in parallel with REC). Studies are categorised as follows:
		  ▪ A: Amendment to a research study that ALL participating NHS organisations are expected to consider.
		  ▪ B: Amendment to a research study that only those participating NHS organisations affected by the amendment are expected to consider.
		  ▪ C: Amendment to a research study that participating NHS organisations are not expected to consider.
		
		• **Gaining MHRA approval** (CTIMP, ATMP and clinical investigations only)**:**
		
		- Provide a covering letter outlining the substantial and any non-substantial changes.
		- Signed notification of amendment form from the European Commission website (CESP). GCP Managers will give access to CESP.
		- Update XML and PDF versions of the clinical trial application form if it has changed since the last submission.

3.	Chief Investigator	**Submit to REC and MHRA once you have sponsor approval.** **Non substantial Amendment** • A valid non-substantial submission to the JRMO is: - All amended documents with track changes. - Completed and signed No Cost Declaration Form. - HRA non-substantial amendment form (see HRA website). - Cover letter to HRA • Once approved by the JRMO, submit amendment to hra.amendments@nhs.net by email using the HRA's Non-Substantial Amendment Form. The MHRA does not need to be notified of non-substantial amendments, these should be filed, recorded in the version control log and submitted with the next substantial amendment or then end of trial notification. HRA does not currently wish to be informed of non-HRA studies. Once sponsor approval is given, distribute to sites as described below. These will not be categorised (HRA categories A, B, C) and should not be implemented until site approval/ agreement is given in writing. **NB: please note that as HRA systems change frequently please look at the latest guidance on HRA website for current processes.** **Await REC, MHRA and HRA approval/categorisation in writing.**
4.	Chief Investigator	**If the HRA, REC or MHRA request further changes to the amendment, seek JRMO Sponsorship approval before replying to the regulators.** • Forward all correspondence with the regulators and additional documents to the JRMO in a timely manner. • Once REC and/or MHRA (as applicable) approvals are in place, forward the approved documents to the JRMO Research Amendments email. • A valid approved amendment is: - Final fully signed amendment form (not draft). - REC approval letter. - MHRA approval letter (where applicable). - HRA Confirmation of Amendment Assessment (Where REC Approval is also required, issue of continuing HRA Approval is conditional on Favourable REC Opinion). - All correspondence with and from the REC/MHRA/HRA. - All amended documents as listed on the REC amendment approval letter. - Written evidence (email) that the CI approves the amendment (if changes were required). - Revised protocols, signed by the CI (CTIMPs only: and Statistician). CTIMPs - All amendments must be approved by the JRMO as Sponsor prior to implementation. For Non CTIMPs Further Sponsor approval is still required, proceed to gaining site approval.
5.	Chief Investigator	**Distribute of amendments to sites and ask request for copies of R&D acknowledgement of the amendment for every site.** Once the HRA have categorised the amendment (A, B or C) the CI should send the Amendment package and categorisation email to participating NHS organisations: • Study Delivery Team • R&D Office at each site • LCRN (where applicable) - If 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/objection raised (conditional on regulatory approval being in place) by the R&D office - If Category C (does not require consideration by site) – Amendment can be implemented immediately after sponsor provides it to the relevant site unless concerns or objection are raised (conditional on regulatory approval)
6.	Chief Investigator	**Update the TMF** • File superseded versions of the amended documents (marking the documents as superseded in pen). • File latest version of the documents in the Trial Master File. • Update the Version Control Log in the Trial Master File. Ensure that the PI signs all new versions of the protocol, and ask for copy of the front page of the protocol as evidence / acknowledgement. If the amendment impacts on the list of source data required by the research site, the CI must send a revised source data list to the PI at all sites for their investigator site file (ISF) and update the source data list in their trial master file (TMF). Notify the JRMO of any issues regarding the implementation of the amendment across any sites.
7.	Chief Investigator	**Provide training if required.** If the amendment requires additional training of coordination staff or site staff, train as appropriate and document in the staff training log (filed in TMF) as applicable
		Halting CTIMPs
8.	Chief Investigator	**When a CTIMP is 'halted' inform the regulators and Sponsor.** If the Sponsor (JRMO) or CI decides to formally halt the trial temporarily, it is the CI's responsibility to notify the MHRA (and REC) **immediately and at the latest within 15-days from when the trial is temporarily halted.** This includes trials where the stoppage was not envisaged in the approved protocol and/or where there is no intention to resume the study. This does not include trials where recruitment may be temporarily halted [short term] for logistical reasons such as trial team unavailability. 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 the trial that has been temporarily halted, the JRMO will immediately make a request that a substantial amendment is made by the CI providing evidence that it is safe to restart the trial. Keep written copies of correspondence to REC and MHRA halting the study and send copies of all correspondence and documents to the JRMO.
		Studies that were approved before HRA processes were introduced.
9.	CI or delegate	**1. Setting up new sites.** If the CI wants to open a new site or a new site type that is NOT listed on Part C of the original IRAS application, this should be approved by the sponsor and then submitted to the HRA (and MHRA where applicable) as an amendment. Ensure the two HRA forms are completed as part of the amendment submission – Statement of Activities and Schedule of Events forms can be found on the HRA website. Adding new sites for pre-HRA approval studies that have not been listed before are considered by the HRA to be: • A substantial amendment for CTIMP

		• And a non-substantial for non-CTIMPs. Follow steps above for substantial and non-substantial submission to sponsor to HRA. The HRA Assessment team will ask for a list of and the current approved document sets (as they do not have access to them). HRA will undertake "assessment lite" to ensure that there are no reasons to prevent the study continuing in the NHS and issue HRA Approval. The CI must share the HRA approval and all study documents with the local site so that they can confirm their capability and capacity to undertake the study at site. These documents should also be sent to the site local R&D office and if the study is on the UKCRN portfolio the relevant local network should also be sent the documents. NB: please note that as HRA systems change frequently please look at the latest guidance on HRA website for current processes. **2. Setting up sites that ARE listed on a pre-HRA Approval study.** If the CI wants to set-up a new site that is listed on Part C of the original IRAS application (or already approved as an amendment) but did not complete the approval process before 31/03/2016, this should be approved by the JRMO as sponsor and then emailed to hra.approval@nhs.net to request that the study transfers to HRA Approval. The submission to the HRA should include a list of the current document set. HRA will undertake "assessment lite" to ensure that there is no reason to prevent the studycontinuing in the NHS and issue HRA Approval. The CI must share the HRA approval and all study documents with the local site so that they can confirm their capability and capacity to undertake the study at site. These documents should also be sent to the site local R&D office and if the study is on the UKCRN portfolio the relevant local network should also be sent the documents. NB: please note that as HRA systems change frequently please look at the latest guidance on HRA website for current processes. **3. Setting up sites that ARE listed on a pre-HRA Approval study.** If the CI wants to set-up a new site that IS listed on Part C of the original IRAS application (or already approved as an amendment), this should be approved by the JRMO as sponsor and then emailed to hra.approval@nhs.net to request that the study transfers to HRA Approval. The submission to the HRA should include a list of the current document set. HRA will undertake "assessment lite" to ensure no reason not to continue in NHS and issue HRA Approval. The CI must share the HRA approval and all study documents with the local site so that they can confirm their capability and capacity to undertake the study at site. These documents should also be sent to the site local R&D office and if the study is on the UKCRN portfolio the relevant local network should also be sent the documents.. NB: please note that as HRA systems change frequently please look at the latest guidance on HRA website for current processes.

List of Associated Documents *(these are standalone documents)*

	Name
Associated Document 1	Confirmation of Costs for Amendments
Associated Document 2	HRA Notification of non-substantial amendment

Change Control. Version 1 to 2

Section Changed	Summary and description of change
All	Corrections of typos.
All	Update of HRA approval process.