Joint Research Management Office Standard Operating Procedure for:			
Study closure for sponsored MHRA-regulated studies			
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Purpose:

The purpose of this standard operating procedure (SOP) is to outline the process that researchers must follow when a Barts Health NHS Trust (Barts Health) or Queen Mary University of London (Queen Mary) sponsored research study has been completed; to ensure that the appropriate regulatory bodies have been notified and that the study is also closed in the Joint Research management Office (JRMO) and archived appropriately.

Scope:

This SOP covers procedures for research teams working on Barts Health and Queen Mary sponsored studies only.

This SOP only applies to studies which are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) i.e., clinical trials of investigational medicinal products (CTIMPs), advanced therapy investigational medicinal products (ATIMPs) and clinical investigations of medical devices. For all other studies, please see *JRMO SOP 18b Study closure for sponsored interventional, research studies and Hosted studies.*

Abbreviations:

ATIMP	Advanced Therapy Investigational Medicinal Product
Barts Health	Barts Health NHS Trust
CI	Chief Investigator

CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
EoT	End of Trial
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Human Tissue Authority
IRAS	Integrated Research Application System
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PI	Principal Investigator
Queen Mary	Queen Mary, University of London
QMS	Quality Management System
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
UKCRN	UK Clinical Research Network

Definitions:

None.

Relevant SOPs:

• SOP 17c	Amendments for sponsored studies (including halting) - Process for researchers
• SOP 18b	Study closure for sponsored interventional, research studies and Hosted studies
• SOP 20	Archiving (transferring research projects to Corporate Records Management)
• SOP 40	Vendor Assessment

SOP Text:

	Responsibility	Activity
1.	Chief Investigator (CI)	**During the study, inform the JRMO if there are any changes to the study that may impact upon when it is due to end.** For example, if there is any change during the study that will impact upon: • When the funding will run out, • Research Ethics Committee (REC) or MHRA approved duration, • The duration the study is active at sites (as per site confirmation or agreements). Any changes to the end of trial (EoT) definition is a substantial amendment and *SOP 17c Amendments for sponsored studies* should be followed.

		Extensions to study timelines may be a minor amendment, but these must be discussed and agreed with the relevant Good Clinical Practice (GCP) and Governance manager.
2.	CI	**Assess whether the study has met the EoT definition and ensure that all study activity is completed within the appropriate timeframe.** The CI must assess whether a study has "ended" by checking the protocol and Integrated Research Application System (IRAS) form ensuring that the study has met the EoT definition and that the study has reached the end points specified in the protocol. Once the EoT definition is reached, the CI has a maximum of 90 calendar days to ensure all aspects of the study have been completed before submitting the appropriate end of study form. For example, all data must be collected and cleaned. "Database lock" must have occurred and be documented. Laboratory work must have been performed as per protocol and samples appropriately transferred to a Human Tissue Authority (HTA) registered tissue bank or destroyed. Once EoT/study notifications are submitted, **no further activity can occur** with the study participants, no amendments can be submitted, no new data or samples collected, and no queries can be issued.
3.	CI / Delegate	**Notify the JRMO of the end of the trial.** For CTIMPs (including ATIMPs) the following documents must be completed and emailed to research.governance@gmul.ac.uk: • Declaration of End of Trial Form (available on the MHRA and Health Research Authority (HRA) websites) • Draft Covering letters to the MHRA and REC For clinical investigations of medical devices, the following documents should be submitted: • Declaration of the End of the Study form (available on the HRA website) • Draft Letter to notify the MHRA of the end of the trial • Draft Covering letter to the REC For all studies working under Confidentiality Advisory Group (CAG approval) • Draft email to CAG as per latest HRA guidance In the email to the JRMO, the CI must confirm that: • EoT definition has been met (with separate written confirmation from the statistician if different from the CI). • Laboratory work is complete. • Site close out visits have been scheduled. • When the statistical analysis will be completed. • Anticipated date for submitting clinical summary report.

		Please allow a minimum of **one working week** for the GCP team to review the end of trial form.
4.	JRMO GCP and Governance Manager	**Review the EoT documentation.** Begin the appropriate study closure workflow in EDGE. Review the EoT form and associated documents for accuracy and completeness. Confirm that: • The EoT definition has been met. • There are no open audits of the study. • There are no open non-compliances in the sponsor's record. • The actual recruitment number matches the sample size, or that any discrepancies are justified. • The study record is up to date on EDGE. • All data has been entered into the study database, all queries have been resolved and the database is locked. • Forward closure notification to jrmo-helpdesk-smdpostaward@qmul.ac.uk Once the review is complete, authorise submission of the documents to the MHRA and REC. Update Status on Green level of EDGE to Closed – follow up completed
5.	CI / Delegate	**Once GCP team authorisation is received, submit EoT form to REC and MHRA (if applicable), and send acknowledgements to the JRMO.** For CTIMPs, the "Declaration of End of Trial form" should be submitted to both the MHRA and REC at the same time. For clinical investigations of medical devices, the "Declaration of the end of a study" form should be submitted to the REC, and a letter confirming the end of the study should be submitted to the MHRA. Please refer to the HRA and MHRA websites (as applicable) for up-to-date information about how and where to submit the Declaration of End of Trial form. The CI must then send a copy of the final signed version of the EoT form to the JRMO along with acknowledgments of receipt from the REC and MHRA. CI must save a copy of the EoT form in the trial master file (TMF), along with all correspondence and associated documentation. The studies public website entry will need to be updated- initially with status and then with full results. For CTIMP/ATIMPs with MHRA approval pre-Dec 2020, the CI or delegate should: • If applicable register for an account on the EU Database on Clinical Trials (EudraCT) website (https://eudract.ema.europa.eu) including a request to be a "Results User". • Send the user information to the JRMO GCP & Governance Manager. • JRMO GCP & Governance Manager will add the user to the study and send an email with the log in details. See *associated document 1 EudraCT result upload flowchart* and *associated document 2 EudraCT upload guidance* for further details.

6.	CI	**Early termination.** Where a study is terminated early (i.e. before the EoT definition has been reached, as defined in the protocol), the EoT form must be submitted to the MHRA and REC within 15 days. Where a study is terminated early, reasons should be given describing follow-up measures (if any) to be taken for safety reasons. Early termination does not include studies that complete earlier than the planned timelines because full recruitment has been achieved. Early termination of a study may be due to reasons other than safety concerns, such as financial or business difficulties of the sponsor or related to slow recruitment. In such cases the CI should contact the JRMO GCP & Governance Manager to discuss their plans prior to submitting the EoT form and cover letter to JRMO for review (include all details as above).
7.	JRMO GCP Team	**Update ReDA, EDGE and the Indemnity folder.** Ensure that the study status is updated to "study closed". Enter the EoT date as the date on the EoT form. Determine the date that the clinical study report is due (one year from the end of the trial) and enter a reminder in ReDA. Complete the EDGE workflow previously started.
8.	CI / Delegate	**International Studies.** Note that the MHRA can be informed, by email, of the closure of UK trial/study sites where other non-UK sites remain active. However, this is separate to their **EoT** notification process. Further details are available on the MHRA website.
9.	JRMO GCP team	**Request information regarding conduct of external vendors.** Once a study (employing an external vendor) comes to an end, a member of the JRMO GCP team should request a statement from the CI/study management team/Clinical Trials Unit (CTU) regarding their interaction with, and service received by, the external vendor during the study. The JRMO GCP team will record this feedback in the "Vendor" spreadsheet located in the electronic Quality Management System (QMS) folder. Any negative feedback should be raised for consideration by the JRMO Contracts Manager and/GCP & Governance Manager, as appropriate. (See *SOP 40 Vendor Assessment* for more details).
10.	CI	**Notify sites, laboratories and facilities of study's closure.** All sites must be sent a copy of the EoT form and REC and MHRA acknowledgements. The CI must provide all sites' Principal Investigators (PI) with the study's closure procedure. The CI must ensure that close out visits are performed. These can be conducted either on-site or via telephone. This is **mandatory** for all Barts Health and Queen Mary sponsored CTIMPs. For close out visits refer to the study monitoring plan or seek guidance from the JRMO GCP & Governance Managers. Only in exceptional circumstances will telephone close out be permitted for CTIMPs. Laboratories must be notified, and instructions given for close down procedures.

		Sites must be given instructions to ensure that all essential study-related material is present and complete for 20 years archiving (as per sponsor policy, see *SOP 20 Archiving*), and are requested to inform the CI and coordinating team of the archiving location. This must include the TMF or investigator site file (ISF), pharmacy file and any study-specific laboratory files.
11.	CI	**Write a Final Report.** CTIMPs and ATIMPs Write a final report for the research study: • Log in into the public database website and enter the details of final report. • Send a PDF draft to the JRMO GCP & Governance Manager (Please see MHRA guidance for content of a final report). ** Please allow a minimum of 2 weeks for the JRMO to review Every report must include JRMO minimum requirements (See *Appendix 1*). All reports must state compliance to GCP and list any deviations to protocol and GCP that have occurred. Send the final report for the research study to the JRMO, main REC and MHRA (initially by submitting it into website 3 weeks prior to the deadline allowing it to be finalised/published **within 12 months of the study ending** and then emailing the finalised version to both parties.**).** Where a study is registered on a public website, e.g. UK Clinical Research Network (UKCRN), it is recommended that a lay report be produced that is understandable to the general public. The final report and acknowledgment by REC and MHRA must be sent to the JRMO and filed in the TMF. Paediatric CTIMPs For paediatric CTIMPs the CI must comply with the timelines set out by European Medicines Agency and submit the Clinical Trial Summary Report **6 months after the EoT**; this can be extended to 12 months if the CI has demonstrated that it is not possible to submit within the timeline for objective scientific reasons. Phase 1 studies on EudraCT- care must be taken as EudraCT will not make Phase I results publicly accessible. Clinical Investigations: **Within 12 months of the study ending,** write a final report for the research study. Every report must include JRMO minimum requirements (See *Appendix 1*) and section 7.3 of ISO14155. All reports must state compliance to ISO 14155 and list any deviations to the protocol and ISO 14155 that have occurred. Send a copy of the draft report to the JRMO via research.governance@gmul.ac.uk. Please allow 2 weeks for the JRMO to review. Once the JRMO have approved submission of the report, email it to the appropriate REC. Ensure acknowledgement from REC is received and forward to the JRMO as per above and file in TMF.

		The MHRA may also request a copy of the final report. If they do, email it to them copying the JRMO for information.
12.	JRMO GCP Team	**Process final report.** In EDGE, log the date that the draft final report is received, the date that it is submitted and the date that it is acknowledged by the regulators. Once report received update Status on Green level of EDGE to Completed and ensure workflow is updated.
13.	CI	**Notify all parties of the study's closure (e.g. funder, public database) and archive your study.** If the research study has been adopted by the National Institute for Health Research (NIHR), upload a lay report to the UKCRN for publication on the NIHR website. Update public databases of results where applicable, e.g. EudraCT, clinicaltrials.gov or similar. If the study protocol/agreement states that participants or other parties will be notified of the study results (e.g. funders or other third parties provided with results of the study), it is the CI's responsibility to send them a copy of the clinical trial summary report, or results. Ensure that all contractual reporting obligations have been fulfilled. Include details of what information was required and when it was reported, e.g. safety reports & study milestones. For studies involving human tissue, all samples must be analysed and either passed to a licensed tissue bank (with appropriate consent and approvals in place) or destroyed prior to the final study report being submitted. For further information please email k.ersapah@qmul.ac.uk Organise research files e.g., TMF to ensure all necessary documents are present and retained. Archive study files following *SOP 20 Archiving*, including participating sites. Discuss archiving electronic data with Corporate Records Manager and the JRMO if applicable. JRMO should be informed that archiving has occurred and of archiving details.
14.	CI	**Publication.** Please See JRMO policy (http://www.jrmo.org.uk/media/jrmo/docs/about-us/our-policies for overarching policy) The sponsor (Barts Health or Queen Mary) must be acknowledged on all publications resulting from a Queen Mary or Barts Health sponsored study. All publications must comply with funder and collaborator publication agreements/terms. In the event that research misconduct or data integrity concerns have been raised, the JRMO, as sponsor along with the senior management of the affected organisation, reserves the right to review, request a hold on publication submission, or refuse permission to publish in discussion. The JRMO as sponsor representative retains the right to review, or request a hold on publication submission, or to refuse permission to publish if there are research misconduct concerns raised, or under investigation, regarding data integrity.

		The purpose of the sponsor review is to ensure that the study data is appropriately represented; it is *not* an additional scientific review. It is meant to be a check that ensures all issues are appropriately discussed (e.g. serious breaches, significant deviations etc.) and that the data being presented can be traced back to the source data. The sponsor has delegated the generation and publication of the study to the CI, but the sponsor is responsible for accurate reporting of the study. In line with the Sponsor to CI agreement the JRMO must be notified of any outputs of the research such as guidelines, publications, presentation, changes in service delivery etc. prior to external submission or presentation. In the event that research misconduct or data integrity concerns have been raised, the JRMO, as sponsor, in discussion with senior management of the affected organisation, reserves the right to review, request a hold on publication submission or to refuse permission to publish.

Change control

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

Section changed	Summary and description of changes
All	Clarification of processes

List of appendices

Appendix ref.	Appendix name
1	Case Study Report: JRMO minimum requirements

List of associated documents

Document ref.	Document name
Associated Document 1	EudraCT result upload flowchart
Associated Document 2	EudraCT upload guidance

Appendix 1: Clinical study report: JRMO minimum requirements

There is no standard format for final reports. The EMA & HRA have produced guidance on content.

As a minimum for all Barts Health and Queen Mary sponsored studies, reports must include:

- **A.** Statement to clearly state if the study's objectives were met.
- **B.** Description of study population.
- **C.** Results/main findings. This should include data as well as a descriptive conclusion.
- **D.** Safety – including all events.
- **E.** Statement of compliance to the UK Policy Framework for Health and Social care research, GCP and the protocol. This should include any deviations to protocol and GCP that have occurred and the impact of these on the data and general compliance.
- **F.** Arrangements for publication or dissemination of the research, including any feedback to participants.

For CTIMPs, compliance with the principles of ICH Topic E 3 Structure and content of clinical study reports is **mandatory**.