Standard Operating Procedure (SOP) for:			
Essential documentation including Trial Master Files and files for all external sites and facilities			
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Purpose:

This standard operating procedure (SOP) describes the process for maintaining essential documentation throughout the life of a clinical trial, as required under Good Clinical Practice (GCP).

The purpose is to ensure that all essential documentation is maintained to allow accurate and robust reconstruction of the trial and ensure verification of the data quality.

Regulation 31A (4) of SI 2004/1031 defines essential documents as:
"*The essential documents relating to a clinical trial are those which (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been conducted in accordance with the applicable requirements of the Directive*".

Scope:

This SOP applies to all research being sponsored by Barts Health NHS Trust (BH) and Queen Mary, University of London (QMUL). It is mandatory for clinical trials regulated by the MHRA i.e. clinical trials of investigational medicinal products (CTIMPs), clinical trials of advanced therapy medicinal products (ATIMPs) and clinical trials of non-CE marked medical devices or medical devices used outside of their CE marked purpose (clinical investigations). This SOP is advisory for all other research.

This SOP must be followed for all new sponsored CTIMP trials set up after the effective date of this SOP. All trials active at the time of SOP release should review their TMF to ensure that all requested documentation is present in their TMF but there is no requirement to migrate existing TMFs / ISFs or central facility files to this format.

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

CRF	Case Report Form
CTA	Clinical Trials Agreement
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
ATIMP	Advanced Therapy Investigational Medicinal Product
QMUL	Queen Mary University of London
QP	Qualified Person (specially qualified pharmacist)
PI	Principal Investigator
PID	Participant Identifiable Data
PSF	Pharmacy Site File
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom

Definitions:

None.

Relevant SOPs:

• SOP 11a	BH/QMUL sponsorship of MHRA-regulated trials: Process for researchers
• SOP 20	Archiving for research projects

SOP Text:

	Responsibility	Activity
1.	Chief Investigator	**<u>Ensure essential documentation is maintained for every trial from set up to archiving.</u>** It is the responsibility of the CI to ensure that all essential documentation is retained, maintained, and updated as needed at all sites and central facilities. Every trial must have a separate and clearly identifiable Trial Master File (TMF) and each site must have an Investigator Site File (ISF) for each trial.
2.	Chief Investigator	**<u>Ensure that the TMF is set up and maintained according to the contents page associated with this SOP.</u>** The TMF must be set up no later than the green light meeting, where it will be reviewed for completeness (see SOP 11a BH-QMUL sponsorship of MHRA-regulated trials: Process for researchers). The TMF must be set up according to associated documents 1 and 2.

		Not all documents will be relevant to every project – the CI may agree the exact contents of the TMF with the GCP team during the set up process. Certain documents such as the protocol and enrolment log are always required. The TMF will be set up before or during the green light process, and the content of the TMF and ISF(s) will be agreed with the sponsor as part of the green light process (see SOP 11a BH-QMUL sponsorship of MHRA-regulated trials: Process for researchers).
3.	Chief Investigator	**Ensure that all sites receive and maintain an Investigator Site File (ISF), including pharmacy and laboratory file(s) where applicable, in accordance with the contents pages associated with this SOP.** Each site should be given an ISF, set up as per the ISF contents page, (associated document 3) or be sent a copy of the contents page to set up their own file. Each site pharmacy should be given a Pharmacy Site File (PSF), set up as per the pharmacy file contents page (associated document 4), or be sent a copy of the contents page to set up their own file. Sites must not be activated until their ISF (and PSF where applicable) are in place. In single-centre trials where a single team is responsible for both trial management and delivery the TMF and ISF may be combined in a single file. This must be approved by the JRMO. Multi-site studies must have a TMF held centrally and ISF at each site, pharmacy, laboratory, and central facility.
4.	Chief Investigator	**Ensure all central facilities receive and maintain a Trial File.** Each central facility should be given a Trial File, or provided with a copy of a contents page to set up their own file. The coordinating team/CI is responsible for ensuring all central facilities are appropriately set up with all essential documentation, logs, and manuals before activation (See SOP 46 Site selection, site initiation and site activation).
5.	JRMO Research Management & Governance Officer	**Set up sponsor file.** Each MHRA-regulated trial must have a sponsor file, held in the JRMO separately to the main TMF.
6.	JRMO Clinical Trial Monitor	**Maintain sponsor oversight file.**
7.	Chief Investigator	**Ensure staff are appropriately trained.** Ensure that all staff within the trial co-ordination team are logged on Co-ordination Delegation Log and their training is logged on trial specific training log (see associated documents). Ensure all sites maintain appropriate delegation and training logs.
8.	Chief Investigator	**Give special consideration to trial correspondence, the IMP sections of the TMF, wet signatures, Participant Identifiable Data (PID), file notes, data, duplication, blinded studies, version control, and storage.**

Correspondence
The conduct of clinical trials generates large amount of correspondence, such as emails, letters, meeting minutes, and telephone call reports.

All relevant correspondence that is necessary for the reconstruction of key activities and decisions, must be retained (GCP Guide Ch 10.3.2). The JRMO GCP team can provide advice on the correspondence that should be retained.

It is recommended by the MHRA that correspondence is effectively organised; for example by topic area and dates or in relevant sections.

IMP sections
The IMP section of the TMF must be reviewed by the Senior Trial Pharmacist who gives final Pharmacy approval on behalf of the sponsor, prior to the green light being given. This will ensure that content page sections such as Qualified Person (QP) release, instructions for handling the IMP, sample labels for IMP, shipping record(s) for IMP, Certificate(s) of Analysis of IMP(s) shipped, IMP accountability at site, IMP(s) destruction records, TSE certifications and temperature control logs (where applicable) are clearly marked as needed or not applicable.

Final documents with wet signatures
Original wet signature documents should be filed in the most appropriate location for the document type, for example, the wet signature Clinical Trial Agreement (CTA) should be located in the sponsor project file, whilst copies should be kept in the TMF and ISF, while the wet signature of the PI on the protocol signature page should be in the ISF.

Contact the JRMO GCP & Governance Managers if unsure.

Participant Identifiable Information (PID)
Unless specified in the approved protocol and REC application, PID must only be stored at site, for example in the ISF of Pharmacy file. All other files (TMF, sponsor file, and other central facility files) must not contain any PID.

Use of file notes
The JRMO file note template is recommended for use and should be distributed to sites and facilities. The TMF should be a stand-alone document set that requires no additional explanation from CI or research team members.

The CI and teams should carefully consider the need for every file note. They are not to be used as an excuse for missing documents or used when other correspondence fully explains an event or occurrence.

Data
Case Report Forms (CRFs) may be stored separately from the ISFs and TMF, but the ISF/TMF must define their location.
At the end of the trial, the original paper copies of the CRFs must be kept at the site and copies can be added to the TMF.

Where electronic CRFs are used, each site must be given a complete copy of their electronic CRFs at the end of the study.

Duplication
Duplication of documents within the TMF is to be avoided (MHRA GCP guide CH 10.10.3.3) as this can hinder effective use of the TMF. Where possible, file only one copy of the document in the appropriate file. For example, where

		annual reports are submitted to numerous parties, one copy should be files in the TMF with the cover letters to each party. **Blinded studies** Special attention should be given to trials involving any form of blinding. Delegation logs should clearly document who is blinded and unblinded. In some cases a separate unblinded section of the TMF may need to be established. **Version control** The CI is responsible for ensuring strict version control of all essential documents and ensuring that all sites receive up to date versions. A version control log must be kept and maintained for all essential documents submitted for regulatory approval. It is recommended that the document version control logs are used (see templates). Any other version control logs used must be approved prior to or during the green light meeting. It is recommended that documents are filed in a sequential order, with the most recent version of the document filed on top. N.B. All amendments need to be approved by the sponsor before sending to the regulators for approval and before implementation (see SOPs 17a, 17b, and 17c regarding amendments). **Superseded documents** When documents are superseded, one complete copy of the old document must be retained in the TMF and ISF, and must be clearly marked as superseded to avoid confusion. This ensures that there is a comprehensive catalogue in each location, and evidence that the site received each up to date version. Where possible the superseded document should be marked with the date and initialled by the person maintaining the documents, along with the document version number of the document superseding it. The version control log must be updated accordingly by the person responsible for maintaining the documents. **Storage** All trial files must be stored in a safe, secure and confidential location that is accessible only by authorised staff (including monitors, auditors and inspectors). As some of the documents within the files will contain confidential data, it is important that they are retained in a secure place with restricted access to the relevant trial staff only. It is considered best practice to store documents within a locked cupboard within a locked room. Consideration should be made to the location (e.g. protected from potential dampness and leaks).
9.	Chief Investigator	**Documents must be filed in a timely manner.** TMFs must be kept up to date in order to comply with the UK regulations. Documentation that is relied upon for subsequent activities should be filed within the TMF before these activities take place, for example emails documenting safety analysis prior to next cohort being started.
10.	Chief Investigator	**Archive documents at the end of the project.** Once the clinical study report has been submitted and acknowledged (for end of trial procedures see SOP 18a Project closure: Process for researchers) the TMF and ISF can be archived (see SOP 20 Archiving research projects).

Change control

This section outlines changes from version **2.0** to version **3.0**

Section changed	Summary and description of changes
2	Addition of CI responsibility to ensure coordination and Site delegation and training logs are used
Template	Addition of template trial specific training logs

List of appendices

There are no appendices for this SOP.

List of associated documents

Document ref.	Document name
1	TMF contents page multi-site
2	TMF site sections
3	ISF contents page
4	Pharmacy file contents page
5	Enrolment log
6	Site delegation log
7	Coordinating team delegation log
8	Protocol version control log
9	PIS, ICF and GP letter version control log
10	Amendment log
11	File note template
12	File note log
13	Training log
14	Deviation log

The JRMO would like to acknowledge the Centre for Experimental Cancer Medicine for its templates that have been used and incorporated to create this SOP.