Standard Operating Procedures (SOP) for:			
Process for Researchers- Essential Documentation including Trial Master Files and Files for all External Sites and Facilities			
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Purpose and Objective:

This SOP describes the essential documentation that must be maintained in a Trial Master File (TMF), as required under Good Clinical Practice (GCP).

The purpose is to ensure that all trial teams retain and maintain essential documentation so that it is available within the study file 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*".

The TMF and Investigator Site Files (ISFs) together are jointly the location of all the essential documentation for the trial. The Chief Investigator (CI) is delegated the responsibility of maintaining the essential documentation in a TMF format.

The CI is delegated the responsibility for ensuring that all sites and central facilities are set up and maintained. This includes opening the site / facility to the study, providing them with all the appropriate documentation when they start working on the study, and ensuring that they receive amended documents and approvals during the study.

Should the CI delegate responsibility to setup and maintain the TMF to a Clinical Trials Unit (CTU), it should be clearly agreed whose SOP should be followed (the Sponsor's SOP or the CTU's SOP). This will be clearly stated in the Sponsor to CTU agreement.

Scope:

This SOP applies to all research being sponsored by Barts Health NHS Trust and Queen Mary University London. It is mandatory for sponsored clinical trials of an investigational medicinal product (CTIMPs) but advisory only for all other research.

This SOP lays out the requirements to hold and maintain a paper TMF for a CTIMP that fall under the remit of the Medicines for Human Use (Clinical Trials) Regulations 2004. BH and QMUL as sponsor do not permit electronic TMFs.

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.

This SOP applies to all requests for BH/QMUL to Sponsor CTIMPs, Advanced Therapy Medicinal Products (ATMPs), Clinical Trials of non-CE marked Medical Devices that are required to notify MHRA before they start and all BH and QMUL staff working on any activity that falls under them. For the purpose of this SOP 'CTIMPs' means all regulated clinical trials including: CTIMPs, ATMP and Clinical Trials of non-CE marked devices.

Abbreviations:

BH	Barts Health NHS Trust
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Agreement
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
NCC	National Coordinating Centre
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
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TMF	Trial Master File
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom

Definitions:

TMF: The central trial file.
ISF: The study file held at research sites, including any files held at central facilities e.g. pharmacies and imaging departments.

Related SOPs and documentation:

The sponsor will maintain sponsor project records, details of this are located in JRMO SOP 10 (JRMO internal filing process).

Please see SOP 11a (BH-QMUL sponsorship - Researchers guide) and SOP 46 (Site selection, site initiation and site activation). For full details of green light meeting and site activation processes.

Please SOP 20 (Archiving research projects) for full details on the archiving process.

Please see SOP 17a, b, and c regarding Amendments.

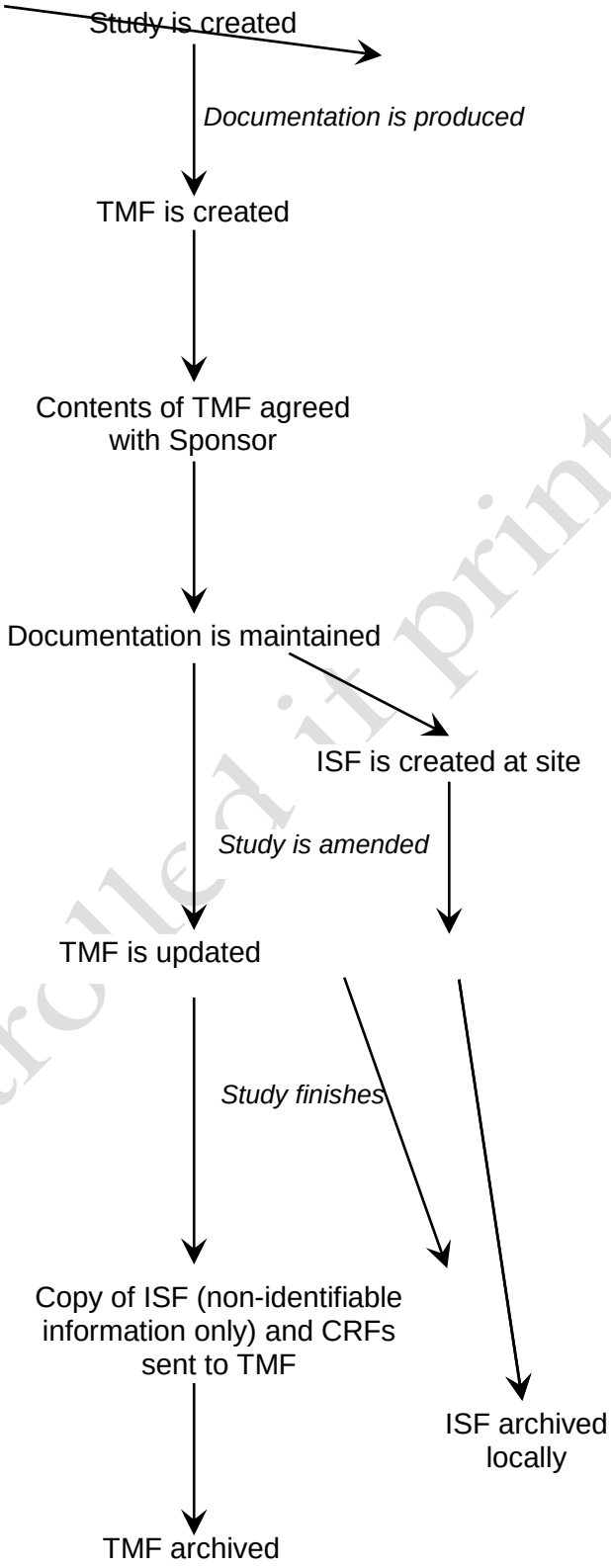
SOP text		
	Responsibility	Activity
1.	Chief Investigator	**Ensure essential documentation is maintained for every trial from set up to archiving.** It is the responsibility of the CI to ensure that all essential documentation is retained, maintained and updated as needed at all sites and central facilities. Every trial must have a separate and clearly identifiable Trial Master File (TMF).
2.	Chief Investigator	**Ensure staff are appropriately trained.** Ensure all staff within trial co-ordination team are logged on Co-ordination Delegation Log and their training is logged on trial specific training log (see templates). Ensure all sites maintain appropriate delegation and training logs.
3.	Chief Investigator	**Ensure that the TMF is set up and maintained according to the contents page (associated with this SOP).** The TMF must be setup no later than the green light meeting (see SOP 11 BH-QMUL sponsorship - Researchers guide). The TMF must be set up according to associated document 1 and 2. Please note that not all documents will be relevant to every project – the content of the TMF will differ depending on the nature of the study. The TMF will be set up before or during the green light process, and the content of the TMF/ISF(s) will be agreed with the sponsor as part of the green light process (see SOP 11 BH-QMUL sponsorship - Researchers guide). The CI will bring the TMF to the final green light meeting for sponsor's review. If not available, this will be checked at an informal monitoring meeting to ensure completeness.
4.	Chief Investigator	**Ensure that all sites receive and maintain an Investigator Site File (ISF), including pharmacy file where applicable, in accordance with the contents pages associated with this SOP.** Each site should be given a file (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 file (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. The coordinating team/CI is responsible for ensuring that all sites (including BH) are appropriately set up with all essential documentation, logs and manuals.
5.	Chief Investigator	**Ensure all central facilities receive and maintain a Trial File.** Each central facility must be given a file. As a minimum the facility must be 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 site activation (See SOP 46 Site selection, site initiation and site activation).
6.	Chief Investigator	**Ensure that the appropriate files are used at each location/site.** If a trial has one single site, the CI may discuss using a joint TMF/ISF with the JRMO. This must be agreed in writing by the JRMO.

		If the coordinating team who are responsible for the trial management are also delivering the research at site, then a joint file TMF/ISF may be used. However if the coordination and delivery team are different, then a separate TMF and ISF must be used. Multi-site studies must have a TMF held centrally and ISF at each site and central facility.
7.	Chief Investigator	**The CI or delegated individual(s) must set up the TMF.** A study file must be prepared at the beginning of the trial and updated throughout the lifetime of the study. The individual assigned this responsibility must be detailed on the delegation log and authorised by the CI. An ISF must be prepared at each site where the research is carried out. The CI will usually delegate responsibility for the maintenance of the ISF to the PI at that site. The PI can then delegate this responsibility, provided the individual is detailed on the delegation log and authorised by the PI.
8.	Chief Investigator	**Special consideration should be given to trial correspondence, the IMP sections of the TMF, wet signatures, Participant Identifiable Data (PID), file notes, data, duplication and blinded studies.** **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 will provide advice on the decisions of where certain correspondence 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 ISF/TMF must be reviewed by the Senior Trial Pharmacist who gives/gave 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, temperature control logs (where applicable) are clearly marked as needed or not applicable. **Final documents with wet signatures** The decision of where to store the final approved document with the original wet signature (for example in sponsor project records (held by JRMO)/TMFs/site files) should be based on the type of document that has been signed. For example, the wet signature on a Clinical Trial Agreement (CTA) must be located in the sponsor project records, whilst copies should be kept in the TMF and ISF. The wet signature of the PI on the protocol signature page should be in the ISF. Contact the JRMO GCP managers if unsure.

		Participant Identifiable Information (PID) Unless specified in the approved protocol and REC application, the location of PID must only be at the site (ISF) and in the pharmacy files. All other files (TMF, sponsor file, and other central facility files) must not contain any PID (but pseudoanonymised data is permissible). **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 trial could be inspected long after the trial team have left the institution, therefore, 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 there must be a reference in the ISF/TMF of 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. When CRFs are electronic, a complete copy of the final locked electronic CRFs must be given to the lead site at the end of a 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 then one copy should be kept, with the cover letters to each party that cite the version submitted to provide clarity as to what was submitted when and to whom. **Blinded studies** Special attention should be given to trials involving any form of blinding. It should be clearly documented who is blinded and unblinded on the delegation log. Agreement should be reached (with JRMO advice) on what documents are in the TMF, considering the potential need for a separate unblinded section.
9.	Chief Investigator	**Ensure documents are version controlled and appropriately stored.** **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 used in all files and locations. It is recommended that the associated template version control logs are used. 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 (see SOP 17a, 17b, and 17c regarding amendments) and before implementation.

		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 which version has superseded 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 trial 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).
10.	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. Documents should be placed within the TMF in a timely manner to comply with this requirement. 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.
11.	Chief Investigator	**The CI is responsible for timely archiving of the relevant documents, and following the appropriate processes.** Once the clinical study report has been submitted and acknowledged (see SOP 18a Process for researchers – end of trial procedures) the TMF can be archived (see SOP 20 Archiving research projects)

Flow Chart



Change Control

This section outlines changed from version 1.0 to version 2.0

Section Changed	Summary and description of change
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 Associated documents

Document	Document name
1	TMF contents page multi-site
2	TMF site sections
3	ISF contents page
4	Pharmacy file contents page

Templates
Enrolment log
Delegation logs (site and coordination)
Protocol version control log
PIS, ICF and GP letter version control log
Amendment log
File note
Training Log
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.