Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	**Setting Up, Maintaining and Archiving Trial Master / Site Master File(s) for CTIMPs**		
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Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Draft v 2.0
Draft v 2.0	10/11/10	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	20/08/12	Periodic Review and Revision of Archiving Process	Final v 3.0
Final v 3.0	21/10/14	Periodic Review	Final v 4.0
Final v 4.0	15/09/16	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) describes the essential documentation which is required to be held and maintained within a Trial Master File (TMF) and/or Site Master File (SMF). It also outlines the requirements for the storage and archiving of trial data.

It is a legal requirement under the Medicines for Human Use (Clinical Trials) Regulations 2004 to have a TMF. In addition, it demonstrates compliance with the DHSSPS Research Governance Framework. Therefore, all University Sponsored/Co-sponsored research involving the NHS/HSC should comply with this SOP.

2. Introduction

The European Clinical Trials Directive was introduced to ensure the standardisation of research activity in clinical trials; the initiation, conduct, recording and reporting of clinical research. As part of this standardisation a minimum list of essential documents has been identified, which must be filed in a timely manner to assist with the successful management of the trial.

A TMF, which is a standardised filing system, should be established at the beginning of the trial i.e. as soon as the protocol is developed. It allows for the effective storage of all documentation relating to the clinical research. It should be noted that not all documents will be of relevance to every project and therefore the content of the TMF, or in the case of multi-centre trials the SMF, will vary from study to study. The various documents are filed into sections as detailed in Appendix 1.

A final close-out of a trial can only be done when the monitor (i.e. the independent assessment of compliance with the protocol) has reviewed both the investigator's and sponsor's files and confirmed that all necessary documents are in the appropriate files.

Direct access for all trial-related records should be made available to the monitor, auditor (i.e. the person who assesses to ensure the trial is conducted in accordance with GCP requirements), Research Ethics Committee or Regulatory Authority (MHRA) on request.

3. Scope

This SOP applies to all studies where the University is acting in the capacity of Sponsor, or lead in a Co-Sponsorship arrangement. It applies to all members of University staff; both academic and support staff as defined by Statute 1, including honorary staff and students.

4. Responsibilities

4.1 Chief Investigator

The Chief Investigator (CI) has overall responsibility for the content of the maintenance of the TMF. The day to day maintenance can be delegated to another member of the research team and this should be recorded on the study delegation log (SOP QUB-ADRE-005). The person responsible will undertake the duties to meet the responsibilities of the Sponsor in relation to the maintenance of all essential documents for the study. It is the CI's responsibility to ensure that the TMF is archived in accordance with EC Directive 2005/28/EC,

the guidance from the European Commission (Eudralex Volume 10, Chapter V) and this SOP.

4.2 Site Principal Investigator

In the event of a multi-centre trial, a Site Master File (SMF) must be set up and maintained by the Site Principal Investigator (SPI) at each participating Centre for each trial. It is the SPI's responsibility to ensure that the SMF is archived in accordance with the agreement in place with the Sponsor.

4.3 Sponsor's Research Governance Project File

As well as the investigator establishing a Trial Master File, the Research Governance Team will also establish a Research Governance Project File. This will contain copies of the relevant regulatory and ethical approvals and the essential documentation required to support these approvals and comply with the DHSSPS Research Governance Framework.

The University's Research Support Office will be responsible for maintaining the appropriate financial information and the Contracts and IP Office will maintain the contractual information associated with the study.

5. Procedure

5.1 Setting up a TMF/SMF: Content and Structure

As soon as an outline protocol has been developed and/or contact made with the Sponsor, a TMF/SMF should be established. The content should comply with the principles of the guidance from the European Commission (Eudralex Volume 10, Chapter 5).

The table in Appendix 1 details the recommended format and content of the TMF/SMF. As a rule, any study related approvals and communication not listed should also be retained. Appendices 2 and 3 are content checklists for the Sponsors TMF and the CI TMF/SMF respectively, which should be held as an index in the file.

A lever arch file(s) is the best format for the storage of essential documentation, though secure filing cabinets can be used. The chosen format should be clearly labelled with the:

- Title of the protocol;
- Protocol number;
- For site specific files, the site name, address and telephone number.

It should be noted that a TMF/SMF may consist of more than one volume. Should this be the case label the files accordingly e.g. File 1 of 3, File 2 of 3 and File 3 of 3.

File the documents in the appropriate sections as detailed in Appendix 1, then in chronological order within each section.

As the project progresses trial documents may require amendment. It is necessary to keep amendments in chronological order indicating the changes made and the dates they are implemented. Old documents/versions must also be retained.

Where certain sections, outlined in Appendix 1, are not applicable to your study, it is good practice to detail a note in the file / section explaining why this section is not required.

5.2 Storage

As the TMF/SMF contains essential original documents and/or confidential data it is important that they are retained in a secure location and in secure conditions. During the study duration, the CI (SPI for multi-centred studies) must retain the TMF/SMF in their main office in a locked filing cabinet/cupboard and the room must be locked.

5.3 Archival

Non-CTIMP studies should be archived according to the relevant University SOP (QUB-ADRE-26). CTIMP studies must be archived according to EC Directive 2005/28/EC, the guidance from the European Commission (Eudralex Volume 10, Chapter V) and this SOP. Directive 2005/28/EC Article 20 states: *"The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request. Any alteration to records shall be traceable."*

Compliance with the detailed guidance available in Eudralex Volume 10, Chapter V on the archiving process should be seen as a requirement of GCP.

Once the study is complete the CI will collate together and ensure that all relevant information required to reconstruct the conduct of the trial should be reconciled in the TMF/SMF, as appropriate. It is recommended that all trial related documents are centrally archived to prevent accident damage, amendment, loss or destruction. Any change in ownership and location of documentation should be recorded in order to allow for the tracking of archived records.

Electronic versions of documentation should be archived using a suitable media and must have controlled access with an audit trail generated. This is to ensure that records cannot be altered after the completion of the trial. When original records are transferred to other media, for the purpose of archiving, the system of transfer should be validated with approval from an appropriate member of the research team in accordance with a defined quality assurance system.

The storage facilities used should be secure and adequately protected from physical damage. The documentation should be retrievable within a reasonable timeframe if requested by the MHRA.

The TMF/SMF is a controlled document and therefore access should be restricted to authorised personnel only such as the study staff, the Sponsor and Regulatory Authorities.

If an investigator becomes unable to be responsible for their essential documents (e.g. due to retirement) the Sponsor must be notified as to whom the responsibility has been transferred to.

The documents to be retained by the investigator may be stored in commercial archives. An archive index / log should be maintained by the Sponsor / contract research organisation to record all TMFs/SMFs that have been entered into the archive, and to track and retrieve documents on loan from the archive.

5.4 Retention of Essential Documents

5.4.1 Trials which are not to be used in regulatory submissions

Essential documents of the Sponsor/trial organisers and investigators, from trials that are not to be used for regulatory submissions, should be retained for **at least five years after completion of the trial**. These documents should be retained for a longer period if required by the applicable regulatory requirement(s), the Sponsor or the funder of the trial.

5.4.2 Trials to be included in regulatory submissions

The Sponsor/or the person with responsibility on behalf of the Sponsor should retain all sponsor-specific essential documents. The retention of these documents should conform with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval(s).

The Sponsor-specific essential documents should be retained until **at least two years after the last approval of a marketing application in the EU**. These documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

The requirements to *Annex 1 to Directive 2001/83/EC* shall be complied with.

In addition the *GCP requirements CPMP/ICH/135/95* apply.

6. References:

International Conference on Harmonisation – Good Clinical Practice (ICH GCP). (last accessed September 2016)

European Commission, Brussels, ENTR/F/2/D (2002) Detailed Guidelines on the Trial Master File and Archiving (last accessedSeptember 2016).

7. Appendices:

Appendix 1 – TMF/SMF Content and Structure

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Essential Documents to be maintained with a TMF

		Located in Files of	
Title of Document	Further Details	Chief Investigator	Sponsor
1. Protocol and Consent			
Final, research protocol and amended protocols with version numbers	To document the Chief Investigator and sponsor agreement to the protocol/amendment(s).	X	X
Confirmation of peer review	To provide evidence that the scientific quality of the project has been independently assessed.	X	X
Example of Informed Consent Form and any amendments	To provide evidence of how informed consent will be logged.	X	X
Examples of any other written information provided to subjects and any updates	To document that research subjects will be given sufficient written information (content and wording) to enable them to give fully informed consent. It should also include any documents the subject needs to complete themselves e.g. diary cards, patient handbook, questionnaire.	X	X
Copy of advertisement for subject recruitment and any amendments	To document that recruitment measures are appropriate and not coercive.	X	X
Copy of any letter/information for a patients GP or consultant		X	X
Investigator's Brochure and updates	To document that relevant and current scientific information about a medicinal product has been provided to Investigators (for example, by the Chief Investigator to Principal Investigators in multi-centre trials)	X	
2. Ethics			
Final Ethics Application and any amendments		X	X
Ethics favourable opinion letter(s).	To document that the trial has received Ethics Committee approval and to identify the version number and date(s) of the approved documents. Approvals to any amendments need to be stored alongside originals.	X	X
Ethics Committee composition where study was approved	To document that the Ethics Committee is constituted in	X	X

(if not already included in ethics approval letter)	agreement with GCP. NB. All NHS Ethics Committees that are approving clinical trials encompassed by the Clinical Trials Regulations will have been granted "authorized" status from the National Research Ethics Service, NRES (formerly COREC) and will therefore work in compliance with GCP.		
Any Ethics Correspondence		X	X
Ethics Reports	For example, annual reports, safety reports, final report by CI	X	X
3. Research and Development			
Trust and R&D application form and approval letter	To document that the trial has received local R&D office approval where the research is being conducted and access to patients in their care as applicable.	X	
Copy of Trust Permissions	To document that the trust has confirmed that the study has approval to begin.	X	X
Copy of financial information relating to the study (funding application/award letter/costings)	To document that financial arrangements for the study are in place.	X	X*
Insurance Statement (copy of certificate/letter/agreement)	To document provisions to the subject(s) for any study-related harm they might experience. This includes cover for negligent and non-negligent harm.	X	X
Copy of sponsor agreement and allocation of responsibilities	To document that a research sponsor has been identified to ensure appropriate arrangements are in place for the initiation, management and financing of the project.	X	X
Copy of any signed agreement(s)/contracts between involved parties	To document agreements and responsibilities for the preparation, conduct and closure of the trial.	X	X**
4. Regulatory			
Regulatory Application Form(s) (if applicable)	e.g. MHRA, PIAG	X	X
Regulatory Authorisation(s) (if applicable)	To document that appropriate authorisation by the Regulatory Authority (such as, MHRA, PIAG) has been issued prior to the project commencing.	X	X
Copy of any correspondence with Regulatory Authority.	To document that due consideration was afforded to the legislation throughout the conduct of the trial	X	X
5. Correspondence (except Trust and Ethics)			
Relevant written correspondence	i.e. letters, meeting notes and minutes, records of telephone	X	X

	conversations, emails.		
6. Research Team – Staff and Training			
Signed and dated CVs evidencing the qualifications of Chief Investigator/research team (or other relevant documents)	To document the qualifications and eligibility of the CI/PI(s) and any key members of the research team to conduct the study, or to provide medical supervision of subjects.	X	X
Delegation of duty log	To document roles and responsibilities of staff for the study	X	
Staff training records	To document any study specific training or general competency training each member of the research team has undertaken	X	
Signature log	To document signatures and initials of ALL persons authorised to make entries or corrections in the CRF	X	
Honorary Contracts for non-NHS Trust staff		X	
7. Participant Information			
Copies of original informed consent forms signed by each project participant	This must include those forms from any screening failures	X	
Master randomisation list	To document the actual randomisation of the trial subjects to different treatment arms	X	
Subject screening log	Required to identify all subjects who entered pre-trial screening even if they were not entered into the study. Document reasons for non-entry as appropriate.	X	
Subject ID code list	To document that the CI/PI keeps a confidential list of all subjects allocated to trial numbers on enrolling in the trial.	X	
Subject enrolment log	To document the chronological enrolment of subjects into the trial	X	
8. Data Collection			
Sample Case Report Form and completion guidance	To document how the Case Report Forms will record information.	X	
Record of retained body fluids/tissue samples (if any)	To document the location of any retained samples if assays need to be repeated	X	
Normal laboratory reference ranges for any tests used or medical/technical procedures included in protocol (includes central labs)	To document the normal values and/or reference ranges of eth test results	X	
Lab/technical procedures/tests certification or accreditation	To document competence of the facility to perform required test(s) and support reliability of results.	X	
Copies of calibration records for technical equipment		X	

9. Serious Adverse Events			
Sample SAE form and copy of reporting procedures	Required for all IMPs	X	
Completed SAE forms (if not included in the Case Report Forms)	Required for all IMPs	X	X
Copies of correspondence from CI to Sponsor/Regulatory Authority(ies) (e.g. MHRA, Ethics) reporting SAEs	Required for all IMPs	X	X
Safety reports	Required for all IMPs	X	X
10. Pharmacy/Product Related			
Instructions for handling of IMP(s) and trial related material(s) (if not included in the protocol)	Required for all IMPs. To document instructions needed to ensure proper storage, packaging, dispensing and disposal of IMP(s)	X	
Sample label for IMP(s)	Required for all IMPs. To document compliance with labelling regulations (EU Good Manufacturing Practice (GMP) Directive) and appropriate instructions provided to the subject.	X	
Shipping records for IMP(s)	Required for all IMPs. To document shipment dates, batch numbers and methods of shipment of IMP(s) and trial-related materials and for tracking of product batch, review of the shipping conditions and accountability.	X	
Certificate(s) of analysis of IMP(s) shipped	Required for all IMPs. To document the identity, purity and strength of any IMP(s) to be used in the trial.	X	
Decoding procedures for blinded trials	Required for all IMPs. To document How, in the case of an emergency, identity of blinded IMP can be revealed without breaking the blind for the remaining subjects' treatment.	X	
IMP accountability at site	Required for all IMPs	X	
IMP(s) destruction record(s)	Required for all IMPs. To document the destruction of any unused IMP(s)	X	
11. Monitoring and Audit			
Record(s) of all monitoring and audit reports	This could include a pre-trial report which documents the suitability of a site for conduct of the trial and also a trial initiation report which documents that trial procedures were reviewed with the investigator and the study staff.	X	X
Final close-out monitoring report	To document that activities required for the study at closeout are	X	X

	completed and copies of essential documents are held in appropriate files.		
Audit certificate (if available)		X	X*
Clinical trial report	Required to document results and interpretation of the trial	X	X

*This information may be held by the University's Research Support Office (Finance Directorate) and not in the Research Governance file held by the Research Governance Team.

**This information may be retained by the Contracts and IP Office (Research and Enterprise) and not in the Research Governance File.