Standard Operating Procedure

ESSENTIAL RESEARCH DOCUMENTS

SETTING Trust-wide

AUDIENCE Research staff responsible for developing, using and maintaining essential research study documentation for research sponsored by UHBW.

ISSUE To describe research study documentation to be maintained for UHBW sponsored studies to ensure compliance with applicable regulations.

QUERIES Contact the Research & Innovation department on 0117 342 9873 or email research@uhbw.nhs.uk

Document History

SOP number	SOP 014	**SOP Version**	2.1
Effective Date	05/NOV/2020	**Review Date**	05/NOV/2022

Version Number	Reason for change
Original V1.0	N/A
V1.1	Minor updates and clarifications. Inserted standard dissemination text at end of SOP.
V1.2	Minor updates and applied new SOP template
V2.0	Major updates to text about sponsor oversight, quality assurance and standards and minor updates elsewhere
V2.1	Minor updates and clarifications as part of biennial review

Review date	Version number	Version date	Effective date	Author/ Reviewer	Authorised by
Original SOP	V1.0	19/OCT/15	03/NOV/15	Diana Benton	Diana Benton
November 2016	V1.1	25/NOV/16	20/DEC/16	Jess Bisset	Diana Benton
23/JAN2018	V1.2	23/JAN2018	22/FEB/2018	Katharine Wale	Jess Bisset
June 2018	V2.0	09/JUL/18	03/SEP/2018	Katharine Wale	Diana Benton
August 2020	V2.1	24/AUG/20	05/NOV/2020	Sandra Mulligan	Jess Bisset

1. Introduction

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments) and Good Clinical Practice (GCP), essential study documentation should be suitably maintained in order to manage the conduct of the research and to enable evaluation of the conduct of the trial, integrity of the trial data and compliance of the trial with GCP. Evaluation may be by audit, monitoring or inspection. The documentation should be stored such that the trial can be accurately reported, interpreted and verified, whilst protecting the confidentiality of the records of trial subjects.

2. Purpose

The purpose of this document is to describe essential trial documentation to be maintained in a Trial Master File. This SOP focuses on the requirements for a clinical trial of an investigational medicinal product (CTIMP). However, most elements will be applicable to all research conducted in the NHS, as part of GCP.

It is recognised that most external trials units will have their own processes for maintaining and archiving the TMF. If an external trials unit has a contract with UHBW which delegates the management of the TMF to the trials unit, UHBW will determine whether the trials unit's internal processes are compatible with the standards set out in this SOP. If acceptable, it may agree to the unit following its own processes and, or, agreement will be sought on alternative processes to be followed, provided that the standards set out in this SOP are maintained. This will take place prior to the study opening to recruitment.

3. Scope

In Scope: Documentation for research sponsored by UHBW. Documentation for CTIMPs sponsored by other organisations where the minimum standards as described in this SOP are not met.
Out of scope: Documentation for research sponsored by organisations other than UHBW.

4. Responsibilities

- The sponsor is responsible for ensuring that a Trial Master File (TMF) is set up, maintained and archived. UHBW delegates sponsor responsibility to the CI (as specified in the Investigator Oversight SOP) for setting up and maintaining the TMF. Day-to-day management of the TMF is usually delegated by UHBW to the trials unit managing the CTIMP. This arrangement is documented in the Division of Responsibilities appended to the agreement between UHBW and the trials unit. For studies not managed by a trials unit (e.g. non-CTIMPs), the responsibility for the day-to-day management of the TMF can be delegated by the CI to a suitably trained member of the trial team.
- For CTIMPs responsibilities for specific tasks in setting up, maintaining and archiving the TMF are also identified in the sponsor's risk assessment, the Study Set up and Management Plan (SUMP) and in agreements with commercial suppliers.
- The Principal Investigator is responsible for ensuring that an Investigator Site File (ISF) is maintained at their site and archived at study completion. The PI retains ownership of the ISF.

5. Abbreviations and Definitions

Abbreviations	
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMS	Document Management System
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust

Definitions	
Trial Master File	The Trial Master File comprises the sponsor file ('sponsor TMF') and the investigator site file ('investigator TMF'). The investigator TMF is usually referred to as the ISF and the sponsor TMF as the 'TMF'. For the sake of clarity, this SOP distinguishes between 'TMF' (when referring to the entire TMF) and 'sponsor TMF'.
Investigator Site File	The ISF is the part of the TMF which is held at the site by the PI.
Sponsor TMF	The sponsor TMF is the TMF, excluding the ISF. The sponsor TMF may be held at different locations and management of the various components of the sponsor TMF may be delegated to various people and organisations, although ultimately it remains the sponsor's responsibility.

6.0 Procedure

6.1 Overview

6.1.1 Management arrangements

- The TMF should be established at the earliest stage possible during study set up.
- For UHBW sponsored CTIMPs and some complex non-interventional studies, the over-arching **management arrangements** of the sponsor TMF will be formally documented before the start of the study in a contract between the sponsor and the trials unit managing the study (where applicable). Further details on management arrangements, including locations of the sponsor TMF, use of paper or electronic format and arrangements for preparing the TMF for archiving will be agreed between the sponsor, the CI and the trials unit managing the study and documented in the Study Set Up and Management Plan (where applicable).

6.1.2 Sponsor oversight of the TMF

- The findings of the sponsor's risk assessment will help determine whether a TMF review monitoring visit is required during the course of the study. If sponsor review is not required, the justification for this will be documented in the risk assessment.
- Completion of UHBW's study closure checklist and evidence of whether the trials unit has followed its own QA processes for maintaining the TMF will help determine whether a sponsor TMF monitoring review and/or a sponsor study close out monitoring review are required prior to archiving. The study closure checklist and the trials unit's QA processes for the TMF will also help to determine whether there are any documents held by the sponsor which need to be transferred to the main TMF.
- Sponsor sign off of the IRAS application form provides evidence of sponsor approval of the protocol and patient documentation. Sponsor review and approval of the application pack is also captured in the EDGE sponsorship workflow.

6.1.3 Investigator Site File

- The documents in the ISF are the TMF documents held at site, which are under the responsibility and control of the PI.
- Any request for access to the ISF by the sponsor must be reasonable and may only be released with the PI or host site's permission.
- *TMPL_044 Investigator Site File Contents* lists the documents that should be included in the ISF for CTIMPs and non-CTIMPs at each participating site. There will be duplicates of some documents held in the ISF and the sponsor TMF. Where UHBW is a host site, the PI should use the sponsor's template (if required by the sponsor) or, if this is not mandatory or not available, should use UHBW's ISF template.

- The ISF should be filed in a location that is easily accessible to all members of the site research team and is held securely to maintain confidentiality of participants' records. The standards set out in section 7 specifically relate to the sponsor TMF, but equally apply to the ISF.
- Source data held within the ISF such as consent forms, screening logs and patient drug accountability records must remain at site unless the participant has given explicit permission for the data to be made available to the sponsor or to other organisations.
- The TMF and the UHBW ISF should be held separately to reduce the risk of compromise to patient confidentiality. Where this is not feasible (e.g. non-CTIMPs managed by the clinical team) and has been agreed with the R&I Department, it may be permissible for the TMF and ISF to be maintained and held together.

6.1.4 E-TMF

- Documents may be held on paper or electronically. The standards described in section 7 below apply equally to paper and electronic filing. It is acceptable to have an e-TMF, provided that it complies with the requirements for security and confidentiality, is readily accessible and mitigating action has been taken against the risk of obsolescence.
- The e-TMF must be validated to demonstrate it has the necessary functionality and that it is fit for purpose.
- There must be evidence of staff training in the use of the e-TMF.
- There must be a documented procedure in place for validating the transfer of documents from paper TMF to e-TMF.
- UHBW has a work programme for the introduction of e-medical records (EVOLVE) across the Trust. The retention period for e-medical records is 30 years after the patient's death. This is longer than current regulations for the retention period for source data. The Trust's e-medical records system has been validated for functionality, including data security, file backup, audit trails, contingency arrangements for systems failure and quality control checks of scanned documents.
- Further information on electronic filing can be found in *GD_018 Essential Research Documentation.*

7. Standards

The TMF should comply with the following standards:

7.1 Completeness

- *TMPL_043 CTIMP Trial Master File Contents Index template* contains the **essential documentation** to be held in the TMF for UHBW sponsored CTIMPs. Depending on the type of CTIMP, some of the documents listed in the template may not be required for that study (e.g. IMP shipping records where IMP is taken from hospital stock). The Contents Index Template includes documents which are not listed as essential documents in section 8 of ICH GCP, such as confirmation of Capacity and Capability, greenlighting of sites, the trial database and database locking arrangements. However, for UHBW sponsored studies these must be included in the TMF as they are necessary for trial management and evaluation. The template is not an exhaustive list and any other documentation not listed in the template but necessary for trial management and evaluation of the trial should also be retained. *TMPL_043* is designed to be used for CTIMPs, but may be modified for use for non-CTIMP studies.
- The TMF should be '**inspection ready**' at all times. Documents should therefore be regularly filed so that the TMF is always up-to-date.
- **Superseded versions** of documents must be retained in the sponsor TMF and ISF to enable trial reconstruction. The ISF should include evidence of receipt and date of implementation. The most recent and current version of documents should be filed at the front of the relevant section of the TMF. Previous, superseded versions should be retained in

the same section, crossed through and marked as superseded. For electronic documents, a 'superseded' folder may be created for storing previous document versions.

- *TMPL_061 Amendment log template for CTIMPs* should be completed to track **amendments** made throughout the study for UH Bristol sponsored CTIMPs. Alternatively, a trials unit may use its own amendment log template, if agreed by sponsor.
- Documents which are relevant to more than one study and are held elsewhere in a **centralised system** must be retained for the full duration of the study archiving period. This includes staff training records and SOPs. The location of centralised documents e.g. SOPs must be clearly stated in the TMF.
- There should be a complete record of individual **staff training and competencies** for the full duration of the study (i.e. evidence that the CI/PI and staff on the delegation log were appropriately trained and with the relevant experience at the time they were responsible for carrying out their duties). If training records, staff CVs and evidence of qualifications are held elsewhere, the location should be clearly flagged in the TMF. If staff records are held centrally, steps should be taken to ensure that these are retained for the duration of the archiving period.

7.2 Accessibility

- Depending on the type of study and its level of complexity, it is acceptable for the TMF to be **dispersed** within and between departments and across organisations. For example, the trials unit may choose to keep separate folders for completed CRFs and for each participating site; the pharmacy department and other support departments at UHBW may hold a pharmacy TMF file and, if the study is managed through an external trials unit, it is likely that the main section of the sponsor TMF will be located within that organisation. The location of dispersed files should be clearly flagged in the main section of the sponsor TMF. *TMPL_043 Trial Master File Contents Index* template provides this facility.
- Consideration needs to be given to **ease of access** to the TMF. Staff who need access to the TMF should know where it is located and should be able to readily access the sections of the file which they need in order to carry out their delegated responsibilities.
- The requirement for accessibility equally applies to electronic filing. **Speed of access** to IT systems also needs to be considered, and the avoidance of any unnecessary delays to access in the event of an inspection.
- Further guidance on how to organise the TMF and facilitate ease of access, may be found in *GD_018 Essential Research Documentation*.

7.3 Legibility

- All documents should be clearly readable. Particular attention should be given to faint type, blurring at edges of documents and unidentifiable signatories.

7.4 Security and Confidentiality

- The TMF should be held securely to protect it from loss or unauthorised access e.g. in a locked cabinet in a locked room within a swipe card protected area.
- There may be some parts of the TMF which should only be accessed by certain staff groups or access prohibited to certain individuals (e.g. for blinded studies). Consideration should therefore be given to, and arrangements put in place, for **controlled access** arrangements to the TMF. Consideration should also be given to who is permitted to add or to remove documentation from the TMF. The e-TMF should be protected from unauthorised changes and there should be documented processes for setting up user accounts, secure passwords for users and use of password protected files.
- The e-TMF should be regularly backed up and there should be a recovery plan in place for potential loss or destruction of data.

7.5 Traceability

- Any changes made to documents should be traceable e.g. through use of version control and documented evidence of authorised changes to documents. With regard to e-filing, this can be facilitated by use of audit trails so that it is clearly visible who has made changes and when the changes were made.

7.6 Quality assurance

- Evidence of quality control checks undertaken by the sponsor and the trials unit must be retained in the sponsor TMF or, if filed elsewhere, the location should be specified in the TMF. This includes annual EDGE study verification of UHBW sponsored CTIMPs, EDGE workflows, validation of documents scanned into the e-TMF and TMF monitoring reviews. QA documents produced by the sponsor which are to be filed in the TMF should be sent to the trials unit for filing contemporaneously.
- It is recommended that the study trials unit carries out a quality control check of the sponsor TMF at least annually. The sponsor may also conduct a sponsor TMF and, or, a UHBW ISF monitoring review if the sponsor risk assessment and the sponsor monitoring plan identifies these as a need.
- Sponsor oversight arrangements, as described at section 6.1.2, are part of the quality assurance arrangements or the sponsor TMF.
- There should be periodic quality control checks of documents scanned from paper to the e-TMF (as applicable); for further information on this topic, see *GD_018 Essential Research Document*ation

8.0 Preparing the sponsor TMF for archiving

- Refer to *SOP_015 Archiving of Research Documentation* on how to archive the sponsor TMF and the ISF.
- The TMF may comprise files which are dispersed across several departments and/or organisations (e.g. pharmacy files and documentation held by commercial suppliers). These should either be brought together as a single file or the location of dispersed files should be flagged in the main TMF.
- When the study is ready to be archived, both the sponsor and the organisation managing the sponsor TMF should check that it includes all necessary **evidence of sponsor oversight**. Sponsor oversight may include, but is not limited to, sponsor review and approval of documentation, sponsor File Notes, monitoring conduct of the trial, maintenance of an SAE/breaches database and EDGE workflows. It is expected that most of this information would be contemporaneously filed in the TMF during study conduct, or that the location of documents or workflows held on centralised systems is flagged in the sponsor TMF as part of study set up.
- If the study is managed by an external trials unit, evidence of its **internal quality management controls** of the study should either be archived in the TMF or the location of this documentation clearly flagged in the TMF.

9.0 MHRA inspection

- The TMF should be readily available for inspection during the trial and for the duration of the specified archiving period.
- It may be necessary for the trials unit managing the sponsor TMF to sends documents to the sponsor to assist MHRA inspection. The trials unit should take steps to assure itself that the documentation reviewed by the inspectors has not been changed during transfer. The MHRA therefore recommends that the trials unit should retain a copy of any material transferred to sponsor**.**

10.0 Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&I) and will be available on the R&I website.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP_007 Research Training UHBW*

REFERENCES	• ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996) – Section 8 • MHRA - Good Clinical Practice (2012) • MHRA Position Statement and Guidance: Electronic health records – V1.0 16 Sept 2015 • GCP Inspectors Working Group of the European Medicines Agency - Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials
RELATED DOCUMENTS AND PAGES	• GD_018 Essential Research Documentation • SOP_007 Research Training UHBW • SOP_015 Archiving of Research Documentation • TMPL_043 CTIMP Trial Master File Contents Index • TMPL_044 Investigator Site File Contents • TMPL_061 Amendment log template for CTIMPs These can be found on the R&I section of UHBW's website: http://www.uhbristol.nhs.uk/research-innovation/
AUTHORISING BODY	Trust Research Group
SAFETY	N/A
QUERIES AND CONTACT	Contact the Research & Innovation department on 0117 342 9873 or email research@uhbw.nhs.uk