The Creation & Maintenance of Trial Master Files & Essential Documentation

Policy Details	
Document Type	Standard Operating Procedure
Document name	KHP-CTO/CT/SOP5.0 The Creation and Maintenance of Trial Master Files and Essential Documentation
Version	Final v 6.1 03Mar23
Effective from	3rd March 2023
Review date	28th November 2025
Owner	King's Health Partners Clinical Trials Office
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Superseded documents	Final v 6.0 18th December 2019
Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 UK Research Governance Framework for Health and Social Care

Change History			
Date	Version Number	Change details	Approved by
9th Nov 2010	2.0	Transfer to Kings Health Partners Livery and inclusion of archiving details.	Jackie Powell
27th Feb 2013	3.0	Change JCTO to KHP CTO and other administrative changes	Jackie Powell
24th Jun 2013	4.0	TMF Index amended and inclusion of TMF check prior to archive	Jackie Powell

28th Nov 2016	5.0	Update of Glossary, scheduled review, inclusion of a section for HRA in the TMF, inclusion of TMF File Review template	Jackie Pullen
1st Oct 2018	5.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
18th Dec 2019	6.0	Scheduled review, minor updates and renaming of the TMF table of contents template to TMF index and subject to participant	Jackie Pullen
03Mar23	6.1	Scheduled review, minor updates	Jackie Pullen

Table of Contents

1.0 GLOSSARY

Case Record Form (CRF) - A printed, optical, or electronic document designed to record all of the protocol-required information to be collected on each trial participant.

Chief Investigator (CI) – A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Research Associates (CRAs) – Part of the KHP-CTO Quality Team. Ensures compliance with the Regulations, GCP and SOPs, by monitoring clinical trials. Oversight of clinical trials on behalf of KHP sponsors for CTIMP studies.

Clinical Trial - Any investigation in human participants, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal product and/or to identify any adverse reactions to one or more such products and/or to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products.

Essential Documents - The essential documents relating to a clinical trial are those which enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and show whether the trial is, or has been, conducted in accordance with the applicable requirements of the Regulations.

Good Clinical Practice (GCP) – As defined in the Regulations.

Health Research Authority (HRA) – An authority in England established in 2011 which exercises functions in connection with the facilitation and promotion of research and the establishment of research ethics committees.

Investigator Site File (ISF) - A standard filing system which contains all essential documents held by Principal Investigator(s) conducting a trial which individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced.

King's Health Partners (KHP) - King's Health Partners Academic Health Science Centre is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas', King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) - Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital NHS Foundation Trust to provide a streamlined approach for all aspects of trial administration.

KHP-CTO Standard Operating Procedures (SOPs) - "Detailed, written instructions to achieve uniformity of the performance of a specific function," SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

Medicines & Healthcare products Regulatory Agency (MHRA) - UK Competent Authority responsible for regulation of clinical trials.

Participant - An individual who consents to take part in a clinical trial. This individual may also be known as a **patient, volunteer or subject.**

Principal Investigator (PI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a site.

Research & Development Dept (R&D) – NHS department responsible for confirmation of capacity and capability for all clinical research.

Source Documentation - Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor - The organisation taking responsibility for the initiation, management and financing (or arranging the financing) in relation to a clinical trial. The Sponsor organisation has responsibility for carrying out the sponsor functions of that trial (as defined in the Regulations).

Statutory Instrument (SI) – Legal means of implementation of EU Clinical Trials Directive into UK law. SI 1031 (2004), subsequently amended by SI 1928 (2006), SI 2984 (2006), SI 941 (2008), SI 1164 (2009) and SI 1882 (2010). This may also be referred to as the Regulations.

Trial Master File (TMF) - a standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular clinical trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside case report forms and source documentation.

2.0 BACKGROUND AND PURPOSE

Regulation 31a of SI 2004/1031 requires that a readily available TMF is kept, which contains the essential documents relating to that clinical trial, whilst demonstrating compliance with the principles of GCP. The filing of essential documents in an orderly and timely manner allows the reconstruction of trial activities and also greatly assists the smooth running of the trial and any future audit or inspection. With the large volume of documentation required for each trial a satisfactory filing system is necessary.

3.0 SCOPE

All clinical trials sponsored by one or more of King's Health Partner Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, will be monitored for GCP compliance and adherence to this SOP.

3.1 Clinical trials sponsored by King's Health Partner Organisations

It is the responsibility of the CI to establish a TMF for each clinical trial they initiate, by utilising the TMF Index template associated with this SOP (see Section 5.1). CIs conducting multi-centre trials, and who themselves are PI at the coordinating site, will also establish an ISF and to do this they will utilise the ISF Index template associated with this SOP (see Section 5.2). For CIs conducting single centre trials, it is acceptable for all documents to be held in one single file which will act as both the TMF and ISF.

CIs for multi-centre trials will ensure a suitable ISF is in use at host sites and should consider providing ISFs to the Principal Investigators at each of the other sites.

3.2 Clinical trials with an external Sponsor

Where there is an external sponsor, the PI may be provided with an ISF for their site with the TMF being held by the Sponsor, If the Sponsor does not provide an ISF, the PI must establish one and may use the ISF template attached to this SOP (see section 5.3)

4.0 PROCEDURE

4.1 Establishing a Trial Master File

The CI will ensure that a TMF is established as soon as possible after an outline protocol is available and/or first contact is made with the trial Sponsor. For multi-centre trials, the CI will keep site-specific sections within their TMF for the essential documents relating to each of the other centres taking part; these will usually take the form of separate site-level files and can be organised according to the ISF Index (see Section 5.2).

The **TMF** will contain the following sections as a minimum requirement:

- Table of Contents
- Correspondence
- Protocol and Protocol Amendments
- Combined Review*
    - Ethics Committee
    - Competent Authority
    - Health Research Authority (HRA) and Local R&D Capacity and Capability
- Financial and Legal Documentation
- Study Site Staff
- Study-related Supplies (including CRF if applicable)
- Participant Information and Consent
- Participant Information
- Pharmacovigilance
- Monitoring
- Clinical Laboratory
- Pharmacy
- Investigator Brochure/SmPC and Safety Alert Updates
- Data Management (Statistics)
- Clinical Study Report

**If the study pre-dates combined review individual Ethics, Competent Authority, HRA and R&D sections should be present*.

The **Trial Master File Index template** (see Section 5.1) details the recommended format and content for a TMF and is included as an example of good practice.

The **TMF/ISF Table of Contents with Description** is a supporting document which acts as a filing plan and describes in greater detail the documents which will be filed in each section of the TMF (see Section 6.1).

4.2 Maintenance and Storage of the Trial Master File

The file will be actively maintained from its establishment until the trial is formally closed. While certain documents, such as the protocol or participant information sheet, may need to be amended during a project, all superseded versions of documents must be retained in the TMF alongside the new amended version(s).

The TMF will be held at the Chief Investigator's site, or agreed delegated location and copies of relevant documents will be kept at participating sites. The TMF will be stored in a locked cabinet or room in a secure area. Access will be by authorised study personnel only.

4.3 R&D (Sponsor) File

A file containing copies of essential approval documents will be held and maintained by the KHP-CTO on behalf of the Partner Organisation acting as Sponsor. These documents may be duplicates of those held in the TMF.

4.4 Establishing an Investigator Site File

Chief Investigators conducting multi-centre trials will establish an ISF for their own centre participating in the trial as soon as they have set up their TMF; this may be kept as part of the TMF but should be clearly identified as the ISF. With assistance from the KHP-CTO CRA (or delegate), the CI may additionally set-up ISFs for all sites participating in the trial.

Principal Investigators at each of the other participating sites will establish (if this is not been done by the co-ordinating site) and maintain their own ISF using the template provided by the KHP-CTO CRA or delegate.

The ISF will contain the same **sections as the TMF** as a minimum requirement, although its specific contents will probably differ. The **Investigator Site File Index template** (see Section 5.2) details the recommended format and content for an ISF and is included as an example of good practice.

4.5 Maintenance and Storage of the Investigator Site File

The file will be actively maintained by the site Principal Investigator from its establishment until the trial site is formally closed. Both the ISF and the available source documentation will be stored in a locked cabinet or room in a secure area. Access will be by authorised study personnel only.

4.6 Trial Master File review prior to Archiving

Archiving will be performed as detailed in KHP-CTO/SOP/4.0 Archiving of Clinical Trial Data and Essential Documentation.

4.7 Archiving of the Trial Master File and R&D (Sponsor) File

Archiving will be performed as detailed in KHP-CTO/SOP/4.0 Archiving of Clinical Trial Data and Essential Documentation.

4.8 Archiving of the Investigator Site File

It is the responsibility of the Local Site Principal Investigator and host Organisation to ensure that the site ISF and all trial essential documentation are archived according to local SOP or policy once the trial has been closed and the final study report produced.

5.0 RELATED TEMPLATES

5.1 Trial Master File Index template

5.2 Investigator Site File Index template

5.3 Trial Master File Review Checklist template

6.0 APPROVAL and SIGNATURE

03 March 2023

Jackie Pullen
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King's Health Partners Clinical Trials Office

Date