1. Introduction

This Standard Operating Procedure (SOP) decribes the effective management of essential research documentation. Essential documentation required for a research study is established at set up, at both at the local investigator and sponsor site. The creation and management of this documentation is critical not only for the set-up of a research study, but also for delivery of the research and ensuring compliance with all necessary legislation.

The Trial Master File (TMF) is defined by Good Clinical Practice (GCP) as being "those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements." The TMF includes not only the records generated by and managed by the trial sponsor, but it also includes the records generated by and managed by the local investigator. The TMF is therefore made up of a sponsor TMF and an investigator TMF (also known as an Investigator Site File (ISF)). Where UHL are a research site and not the sponsor, the local PI will keep an Investigator Site File (ISF). Where UHL is the sponsor, there will be an ISF but also the sponsor TMF and these files are often combined and referred to as the Trial Master File.

The documentation generated during the conduct of a study can be quite extensive, therefore effective organisation within the TMF and the ISF is essential to facilitate audit and inspection and to ensure effective trial management.

Section 8 of ICH-GCP defines essential documents for the conduct of a clinical trial, although this is not exhaustive.

2. Scope

This SOP should be followed by all staff involved in conducting research at UHL, whether UHL is a sponsor or a participating research site.

3. Responsible personnel

It is the responsibility of the Chief Investigator (CI) for UHL sponsored studies to establish a TMF for each clinical trial they initiate, by utilising the TMF Index template associated with this SOP. It is also the CIs responsibility for maintaining, storing and archiving this TMF.

The local Principal Investigator (PI), where UHL is a participating site research but not the sponsor, is responsible for setting up, maintaining, storing and archiving an ISF using the template associated with this SOP or one provided by the sponsor.

4. Procedure for managing ISFs where UHL is a research site and TMFs for sponsored studies

Please note, the following roles and responsibilities can be delegated to another appropriately qualified member of the local study team providing this is recorded in the Delegation Log. The CI/PI however retains overall responsibility for their roles.

4.1. The local PI is responsible for setting up, maintaining, storing, and archiving the ISF. The CI is responsible for setting up, maintaining, storing and archiving the TMF, in conjunction with the sponsor.

4.2 The ISF will be set up using a template ISF Index as guided by the sponsor organisation or the ISF template linked with this SOP. The TMF will be set up using the index linked with this SOP for UHL sponsored research trials. Most ISFs and TMFs are a mixture of electronic and paper. It is essential that the index (or an alternative document) specifies the location of all essential documentation. File notes must be used to give details of any missing or unavailable documents.

4.3 Only key essential documents, in relation to the clinical trial should be filed, allowing reconstruction of study participation, along with key decisions made during the course of the study.

4.4 There is no requirement at UHL (unless requested by an external sponsor) to print and store paper copies of documentation that are not required for the day-to-day management of a study, where this is located electronically elsewhere (such as on the EDGE database system), for example staff CVs, GCP certificates and contracts. A note on the index and a file note in the relevant section of the ISF to signpost to Edge is sufficient.

4.5 The PI/CI/delegate should file documents promptly and file superseded documents in the appropriate section of the ISF, marked as "superseded", adding an initial and a date. For superseded documentation stored electronically, these should be located in an alternative folder labelled as superseded or archived.

4.6 The PI/CI/delegate should ensure documentation is filed in reverse date order unless specified otherwise.

4.7 The local CI/PI or delegated individual should carry out regular checks to ensure the contents of any TMFs or ISFs are up to date and maintain a record of these checks. It is expected that all ISFs and TMFs are inspection ready at all times.

4.8 The ISF or TMF should be held in a secure location with access restricted to the local study team, R&I and designated representatives of the sponsor. Access will also be granted to auditors and monitors appointed by the sponsor and regulatory inspectors as applicable. The CI/PI must be able to demonstrate that all reasonable measures have been taken to ensure the secure storage of an ISF or TMF in order to protect confidentiality and data integrity.

4.9 The CI/PI should arrange for appropriate archiving of the TMF/ISF as applicable, according to the requirements of the sponsor and appropriate regulatory authorities.

4.10 Where there is a separate pharmacy file, this remains part of the TMF or ISF but can be stored separately in pharmacy whilst a trial is open.

4.11 Please refer to R&I archiving policies and procedures for the archiving of research documentation.

5. R&I files and records

5.1 R&I holds research documentation centrally for all trials. All study documentation is stored on the EDGE system, as per the filing structure in the documents section of the system.

5.2 Research delivery and management teams within the clinical management groups can manage their study documentation as appropriate, however EDGE is preferred as the primary source of all most recent study documentation (whether this is regulatory approved documentation or other study documentation). All study documentation must be stored in EDGE in real-time. Versions of documents must be filed utilising the 'upload a new version' option so that the documents of the same type are stacked rather than filed alongside.

5.3 Research delivery and management teams within the clinical management groups can store study documentation from Edge in alternative locations, providing there are checks in place to ensure documentation matches Edge whenever documentation is updated. Or if an alternative location for the most up to date study paperwork is to be arranged, R&I must be notified and access granted. The local team are responsible for ensuring this documentation is is up to date and filed accurately.

5.5 Where possible the file name of all documentation should be named as follows;

Document name – version XX – Date XX/XX/XXXX – Edge number

6. Procedure for the management of amendment documentation for all trials

6.1 Amendment paperwork should be filed in a folder in the amendments folder at the red level on EDGE whist the amendment is under review.

6.2 Once the amendment has received Confirmation of Capacity and Capability, the approved study documentation should be copied into the relevant folders. For example, the new version of the protocol should be copied into the protocol section ('stacked' on top of the old version as described in 5.2). The amendment documentation can remain in the amendments folder. This will ensure that personnel will only ever access the most recent versions of all relevant study documentation.

7. Version control

7.1 All documents must be version controlled and signed and dated where applicable. They should also have the EDGE and IRAS number on each page where possible. Superseded documents must be easily identifiable as superseded; electronic documents should be labelled superseded or filed in a superseded folder, paper documents should have a single strike through and have superseded written on with a signature and date.

7.2 It is recommended to use the version control tracker linked to this SOP.

8. Supporting Documents and Key References

ICH GCP - 8. Essential documents for the conduct of a clinical trial: ICH E6 (R2) Good clinical practice

9. Appendices

Appendix 1; Version control tracker

10. Key Words

Research, Innovation, Investigator Site File, Trial Master File, Good Clinical Practice.

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

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