UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

NHS Great Ormond Street Hospital for Children Research and Innovation

DIVISION OF RESEARCH AND INNOVATION

Joint Research and Development Office

Document Number: GOSH/ICH/SOP/R&D/003	Version Number: 6
Title: **ESSENTIAL DOCUMENTS FOR TRIALS MASTER FILE AND INVESTIGATOR SITE FILE FOR GOSH-SPONSORED TRIALS**	
Effective Date:	07-07-2021

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1. Scope

This SOP is applicable to all the clinical trials sponsored, co-sponsored by Great Ormond Street Hospital. The SOP is applicable to Chief Investigators (CI), PIs, and delegated trial team members involved in Trust-sponsored CTIMPs and the Joint R&D Office Clinical Trials Team with responsibility for performing sponsor activities on behalf of the Trust. For hosted trials taking place at GOSH, the Sponsor of that trial will be responsible in advising the PI on which documents need to be filed in the Site File.

2. Purpose

This SOP is to inform the Chief Investigator (CI) or the delegated research team member and Joint R&D office Clinical trials team that documents will collectively be referred to as the TMF for Clinical Trials of an Investigational Medicinal Product (CTIMP) that is sponsored by GOSH/ICH. It is a legal requirement to maintain a TMF for clinical trial of investigational medicinal product under clinical trial regulation. It is also a requirement of UK policy framework for health and social care.

3. Definitions/Abbreviations

Essential documents are documents, which individually and collectively permit evaluation of the conduct of a trial, and the quality of the data produced. They demonstrate compliance of the Investigator, Sponsor and Monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. They are to be filed in a timely manner to assist in the successful management of the trial by the Investigator, Sponsor and Monitor. Essential documents may also be audited by the Sponsor's independent audit function and inspected by the regulatory authorities including MHRA to confirm the validity of the trial conduct and the integrity of data collected. Essential documents are collated before the clinical phase of the trial commences, during the clinical conduct of the trial and after completion or termination of the trial.

The planning, conduct and reporting of a clinical trial can generate extensive documentation, which includes internal documents generated by the organisation as a result of following its written procedures as well as documents produced to meet regulatory requirements.

A Trial Master File (TMF) is the collection of essential documentation that supports the conduct and integrity of the clinical trial and data. It is also a form of documented compliance of the trial with GCP. The documentation should adequately reconstruct the trial activities undertaken, along with key decisions made concerning the trial. The Joint R&D Office has access to an electronic TMF (eTMF), where all essential documents stored and maintained.

An Investigator Site File (ISF) is a collection of essential documentation, similar to the documentation found in the TMF. However, it is to be in possession by Investigator of the participating site. ISF may have files that are kept separately in other departments like Pharmacy, Radiology or Laboratory File. A file note should be kept in the main ISF/TMF to establish the location of these folders.

For GOSH-sponsored single centre trials, the TMF and ISF may be the same entity it is maintained by the study team.

Sponsored trials – The organisation who takes the ultimate responsibility of conducting clinical trials. In this SOP sponsor refers to all studies sponsored by GOSH and GOSH R&D act as sponsor representative.

Hosted trials - Any clinical trial where GOSH/ICH is not the sponsor and conducted at Great Ormond site is considered as hosted trial studies. In hosted project, you will need to liaise with CRA appointed by the sponsor.

4. Responsibilities

For GOSH-ICH Sponsored CTIMPs:

4.1. The CI or delegated member of the research team is responsible for:

4.1.1. Set-up and on-going maintenance of the TMF.

4.2. The CI or delegated member of the research team are responsible for:

4.2.1. Maintaining the on-site ISF of the trial.

4.3. The sponsor may delegate TMF maintenance task to CRO/CTU under a clinical trial agreement.

5. Procedure

5.1. Before the trial commences

The CI or delegated member of the research team will create the TMF (please see Appendix 1: Trial Master File Structure Multicentre. The study team/sponsor should ensure all documents stated in Appendix 4: Essential documents Checklist are present as applicable to the minimum. The checklist review is an ongoing process.

For single sites, the CI or delegated member should set up a single file, which will serve as a TMF/ISF (please refer to appendix 2: Trial Master File Structure Single Site)

For multicentre trials, each PI or delegated member should set up the ISF (please refer to appendix 3: Investigator Site File Structure)

The Joint R&D Office Clinical Trials Coordinator will perform a review of the TMF / ISF at the trial initiation visit (TIV) on site or remotely, once confirmation of all necessary approvals and other trial documentation are in place.

If TMF responsibility is outsourced/delegated to an external party, the R&D clinical trial team will maintain the sponsor oversight file. The sponsor oversight file is to demonstrate that sponsor was routinely involved in the project oversight and have their input when it required. The sponsor oversight file content should also present in TMF. For e.g. If an amendment tool is reviewed as part of the amendment process, the signature on amendment tool itself demonstrate sponsor oversight. The sponsor oversight file should contains decision made by the sponsor. For e.g. amendment reviews, input on safety issues, trial progress updates, monitoring reports review, study halt/restart etc.

5.2. During conduct of the trial

The Investigator must ensure that the TMF/ISF is/are continually maintained until the trial is formally closed and final report is submitted.

The CI or delegated research team members will ensure that these regulatory files are organised, complete, accurate and stored appropriately in a secured location with restricted access. The Sponsor will check these files during routine monitoring and any omissions or errors will be written up as findings that must be addressed. The Investigator must maintain the TMF, ready for routine monitoring and potential audit and inspection.

Although ultimately the Sponsor remains responsible for the documents of a trial, the accuracy, completeness and legibility of such documents will be the responsibility of the CI, which is outlined in the sponsor-CI agreement. As part of this procedure, the investigator also holds the responsibility of providing the Joint R&D Office with updated/amended documents. All documents must be dated and version controlled. Any

alterations to documents will need to be traceable. All the documents should be filed chronologically in each section to enable the easy access of recent documentation.

Any additional documentation created or received over the course of the study will be filed appropriately. All original documents will be maintained and revised documents will be added to the study binder. In case of any amendment in the study documentation, superseded documents must be retained in the TMF/ISF but scored through by placing a line to indicate that the document is no longer in use. Superseded documents must not be destroyed.

If documents are held separately to the TMF/ISF, a file note should document the location of the documents and be filed in the TMF/ISF.

5.2.1 Pharmacy and Gene-therapy related Documentation

Documents related to IMP management and accountability may be stored separately in the Pharmacy file. However, if pharmacy are not involved in the management of the IMP/placebo/comparator etc. then the file may be filed with the TMF. The TMF should contain a file note if any file is maintained in a different department.

For Advanced Therapy Investigational Medicinal Products, batch manufacturing records (BMR) are the IMP folders and they will be kept at the Gene Therapy Office with the QA Manager.

5.2.2 Media of Documents

Essential documents are generally in paper format; however they may be stored electronically. The media used to store documents needs to be such that those documents remain complete and legible throughout the required period of retention and can be made available for monitoring, auditing and inspection purposes. Appropriate file notes should be filed in the TMF to state the location of electronic documentation.

5.2.3 Sponsor R&D folders

The Joint R&D Office Clinical Trials Team keep the essential documentation on ReDA, which may duplicate the documents in the TMF. However, all original documentation should remain in the TMF with the CI. The R&D Office hold the sponsor oversight file.

5.3. After completion or termination of the trial

5.3.1. Review of Documentation

It is the responsibility of the CI to notify Joint R&D Office Clinical trials team of the declaration of the end of study as specified in the GOSH End of Study Reporting Requirements SOP. It is important to note that all clinical trial documents belong to the Sponsor. The Monitor should review all essential documentation for accuracy and completeness during the close out visit as specified in GOSH - Monitoring CTIMPs

SOP. The Monitor should also utilise Appendix 5: Close Out Essential Documents Checklist which will assist with the process.

5.3.2. Storage and archiving of documents

All documents will need to be stored in a secure and safe manner, with limited access and also ensure full confidentiality. If the folders are transferred to any sites or vendors then transfer of ownership should be documented in an appropriate agreement with the vendor and also captured in an essential document management plan for such cases. All electronic documents must be stored on the GOSH or ICH server. No documents should be stored on a personal laptop.

5.3.3. Archiving of TMF

It is the responsibility of the Chief Investigator to ensure the all the essential documents that are used to conduct the trial are archived appropriately. All trial-related documents will need to be archived for a minimum of 25 years after the end of trial, but for longer if stated otherwise in the clinical trial agreement. In trials involving GOSH patients, the GOSH policy dictates that all medical documents will need to be archived for 25 years. For advanced therapy medicinal product trials, Batch Manufacturing Records and any other records relating to the full traceability of the IMP should be archived for 30 years after the expiry date of the product or longer if required by the clinical trial authorisation.

For archiving arrangements, the investigator should to contact the Joint R&D Office who will assist with the archiving procedure according to the GOSH Archiving SOP. If there is a change in PI or upon retirement of the PI prior to the end of retention of documents then Joint R&D Office should be informed of the change and they will arrange the transfer of ownership.

5.3.4. Archiving of the Site Files and Pharmacy Documentation

It is the responsibility of the Site PI to maintain the Site file throughout the study to the formal close out. Once the final study is closed, the PI can arrange the site file to be archived locally according to the site procedures. It is the PI's responsibility to make sure that pharmacy folders are archived together with the Site File

6. Related Documents

Document Name
Appendix 1: Trial Master File Structure (Multicentre)
Appendix 2: Trial Master File Structure (Single Site)
Appendix 3: Investigator Site File Structure
Appendix 4:Essential Documents Checklist
Appendix 5: Close Out Essential Documents Checklist

End of Study Reporting Requirements SOP – GOSH/ICH/16/CT-14
GOSH Archiving SOP * GOSH/ICH/SOP/R/004
*GOSH Monitoring CTIMPs SOP *GOSH/ICH/SOP/R&D/006.*

** Also available on the GOSH website or on Q-Pulse as appropriate*

7. References

Good Clinical Practice Guide, Compiled by the Medicines and Healthcare products Regulatory Agency (2012)

Statutory Instrument 2004 No. 1031. The Medicines for Human Use (Clinical Trials) Regulations 2004. The Stationary Office Limited. ISBN 0110490487.

Statutory Instrument 2006 No. 1928. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006. The Stationary Office Limited. ISBN 0110748611.

ICH E6 (R2) Good Clinical Practice

HRA UK policy framework for health and social care research

8. Appendices (If applicable)

Not applicable