1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for managing documentation (paper and electronic) from a clinical drug trial, including the creation, updating, and archiving of trial documentation.

This SOP ensures compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP Legislation and Guidelines.

2 SCOPE

This SOP is valid for all clinical drug trials sponsored by hospitals that have implemented NorCRIN SOPs.

3 RESPONSIBILITIES

Sponsor has the overall responsibility for clinical drug trial documentation and must file all required documents including any updated versions.

The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf. Transfer of duties shall be specified in a written agreement.

The coordinating investigator should ensure that the Trial Master File (TMF) contains the essential documents to be archived by the sponsor. These documents are the property of the sponsor. It is the coordinating investigator's responsibility to create, store and update the TMF. These tasks can be delegated. The delegation of tasks shall be documented.

If the trial is a multicentre trial involving more than one health facility / institution, the coordinating investigator will manage the TMF for the trial, which includes documents from each trial site (health facility / institution). In addition, there will be an ISF at each trial site.

Investigator's Site File (ISF) contains the essential documents to be archived by the principal investigators (PI). The sponsor is responsible for providing the PI with an ISF, and the PI is responsible for creating, storing and updating the essential documents throughout the trial.

The sponsor institution and the institution where each PI is employed should maintain an overview of where the TMF/ISF(s) are located and ensure that they are retrievable, complete, legible and accurate during the entire archiving period. The sponsor institution should also ensure that any electronic systems used for study archiving are validated, and that the validation documentation is kept on file.

4 PROCEDURES

4.1 General principles

The trial documentation is divided into a sponsor part known as TMF and a site-specific part known as ISF. If the trial is a single centre trial, the essential documents in the TMF and the ISF may be filed together, which means that two separate files are not required.

The completeness of the study files will be reviewed during the monitoring visits and possibly during a GCP inspection from the authorities and/or audit by the sponsor.

Trial documentation can be paper only, a combination of paper and electronic documents, or only electronic. If using an electronic file, the system should be able to track who did what and when in the documents.

If an electronic TMF (eTMF) is used, the following requirements should be fulfilled:

- Permissions are based on features / roles
- Access control (audit trail) should be in place to identify the date/time/user who has created, uploaded, approved and changed a document
- The system should be validated, and validation documentation should be stored in eTMF
- Users should be trained, and training should be documented and stored in eTMF

When paper documents are scanned to be stored in an eTMF, the originals may be disposed of after scanning, but the following requirements must be met:

- The file name of the document must clearly describe the content, and contain the scan date and version number, if applicable (e.g. creation date, the document name, version)
- The image quality should be satisfactory
- The number of pages must match the original

These requirements must be checked for each scanned document before the original is disposed of. The same procedure can be used for scanning of wet-ink signatures.

4.1.1 Contents

The essential documents to be kept in TMF are those listed in Chapter 8 of the ICH GCP and other trial-related records that permit evaluation of the conduct of the trial and quality of the data produced (e.g. data management, statistics, protocol deviations, the source data list, etc.).

The structure of the TMF has the following sections:
1. Trial Management
2. Central Trial Documents
3. Site Management

If essential documents are not kept in the ISF, a note describing where they are kept must be filed, see Location of Document if not in ISF.

Superseded versions of documents will be kept in the TMF. Superseded versions of documents provided by the sponsor (e.g. trial protocol, Investigators Brochure (IB)/ Summary of Product Characteristics (SmPC) and eCRF) should be present in the ISF in a manner to enable reconstruction without the need to access the TMF, with evidence of date of receipt (e.g. email or download from a web site), review and/or approval (when necessary) and date of implementation by the principal investigator.

Correspondence must be complete, for example it is not sufficient to file the approval letters from authorities if it does not specify what was approved.

4.2 Before trial start-up

Review section 4.1.

The TMF and ISF should be prepared by the coordinating investigator before the recruitment of the first trial subject. Table of contents templates for the Trial Master File and the Investigator's Site File for multi-centre trials, or if relevant the template for the combined TMF/ISF for a single centre trial, should be used.

There are templates for documents that are included in the TMF (see attachments). It is recommended that these templates are used to ensure that these essential documents are created according to ICH GCP.

The most important documents that should be filed in TMF / ISF are the following:

- Protocol and all protocol amendments, dated and signed by Sponsor
- Patient information sheet and informed consent forms (originals and revised versions)
- Example of the blank CRF
- Source Data List
- Contact Information Study Team, including the Delegation Log
- CVs and documentation of ICH GCP-training for investigators and CVs for other study personnel
- Insurance certificate (Drug Liability Association, Legemiddelansvarsforeningen)
- Approvals, applications and correspondence through CTIS with competent authorities (e.g. Norwegian Medicines Agency (SLV)) and independent ethics committees (IEC, e.g. Regional Committees for Medical and Health Research Ethics (REK)) and internal approvals etc.
- Investigational Medicinal Product (IMP) documentation (e.g. preparation, management).
- Reference values, e.g. laboratory and technical procedures
- Trial initiation report
- Agreements and contracts
- Relevant correspondence allowing reconstruction of important trial activities and decisions, or that contains other significant information

And in the TMF only:

- Data Management Plan
- Statistical Analysis Plan for open studies
- Monitoring plan

Randomisation lists should be kept with restricted access based on roles to ensure that the randomisation and/or the blinding of the trial are kept, see SOP Randomisation, Blinding and Unblinding.

And in the ISF only:

- The Screening Log and Identification and Enrollment Log
- The right accountability form, see attachment, should be chosen and possibly adapted
- Laboratory sample storage overview

4.3 During the trial conduct

4.3.1 Updates

The contents of the TMF and ISF must be updated each time a change occurs in the documents on file. Any change in the documents should be traceable. The documents to be filed/updated in the TMF are reflected in Checklist Conduct of Clinical Trial Sponsor, similarly in Checklist Conduct of Clinical Trial Centre for ISF.

The Sponsor should keep unblinded adverse event data with restricted access based on roles to ensure that the randomisation and/or the blinding of the trial are kept, see SOP Randomisation, Blinding and Unblinding.

It is important to update the TMF/ISF continuously. The monitor will check the completeness of the ISF during monitoring visits.

4.3.2 Storage

Review section 4.1.

The TMF, both electronic and paper documents, should be kept secure and with restricted access by the Sponsor/project leader/PI.

Only trial team members, monitors, auditors and inspectors should have access to the TMF. The Identification and Enrollment log and any other document (e.g. informed consent documents) identifying the trial subjects should be kept separate from the collected data (CRF/eCRF).

Any copies of patient records must preferably be shredded after monitoring visits.

Important emails/communication should be stored with information about sender, recipient, and date. It is recommended to have a specific folder in the email system for emails that should be printed out and filed in the TMF/ISF.

4.4 Close-out

Review section 4.1

At the end of the trial the TMF/ISF must be updated before long-term archiving. See also SOP Completion, Reporting and Archiving.

Any copies of patient records must be shredded at the end of the trial and not included in the archived TMF/ISF.

Important emails/communication should be stored in the TMF / ISF with information about sender, recipient, and date.

Duplication of documentation should be avoided.

The medium chosen for archiving (i.e. paper or electronic) should be documented on the tables of content of the TMF/ISF by putting a check mark in the appropriate column. If an electronic system is chosen, paper documents should be scanned as described under section 4.1. The certification of the scanning should be documented at the end of the tables of content of the TMF/ISF.

Only trial team members, monitors, auditors and inspectors should have access to the TMF. The Identification and Enrollment log and any other document (e.g. informed consent documents) identifying the trial subjects should be kept separate from the collected data (CRF/eCRF).

Sponsor/PI will archive the TMF/ISF for at least 25 years after the trial is completed, in accordance withreg 536/2014. For advanced therapy trials the documentation should be stored for 30 years, please refer to SOP GCP for Advanced Therapies. There is no requirement for documentation to be archived on-site, however the TMF shall be archived in a way that ensures that it is readily available and accessible, upon request, to the sponsor, auditor and monitor.

The Sponsor/PI/coordinating investigator shall ensure that there are procedures to protect the documents throughout the archiving period.

5 MANAGEMENT OF NON-COMPLIANCE

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution. Protocol deviations should be reported according to the trial protocol or the Protocol Deviation Handling plan.

6 REFERENCES

6.1 External references

- REGULATION (EU) No 536/2014 of The European Parliament and of the Council on clinical trials on medicinal products for human use, Articles 57 and 58.
- ICH Guideline for Good Clinical Practice (ICH GCP) E6 (R2) - chapter. 8.
- Eudralex, Volume 10
- EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)

6.2 Internal references

- SOP Protocol Deviation Handling
- SOP Completion, Reporting and Archiving
- SOP GCP for Advanced Therapies

7 ATTACHMENTS

- Checklist Conduct of Clinical Trial Sponsor,
- Checklist Conduct of Clinical Trial Centre
- Trial Master File (TMF) Table of Content Multicentre Trial
- TMF Index Divider Multicentre Trial
- Investigator's Site File (ISF) Table of Content
- ISF Index Divider
- TMF/ISF Table of Content Single Centre Trial
- TMF/ISF Index Divider Single Centre Study
- Location of Document if not in ISF
- Informed Consent Form Version Tracking Log
- Protocol Version Tracking Log

- Contact Information Study Team
- Meeting Participants List
- Prescreening Log
- Screening Log
- Identification and Enrollment Log
- Laboratory Sample Storage Log
- Source Data List
- Pharmacy File Table of Contents
- Delegation Log
- Training Log
- Investigator Curriculum Vitae
- CV- for Non-investigators

8 DEFINITIONS

SOP Definitions.

Abbreviation	Term
GCP	Good Clinical Practice
eCRF	Electronic Case Record Form
CI	Coordinating Investigator
CTIS	Clinical Trial Information System
CV	Curriculum Vitae
CRO	Contract Research Organisation
IB	Investigators Brochure
ICH	International Conference on Harmoisation
IMP	Investigational Medicinal Product
ISF	Investigator's Site File
PI	Principal Investigator
TMF	Trial Master File
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

9 CHANGES SINCE LAST VERSION

CT SOP version no 1.0

Main changes from LM SOP 2.05 Adapted to the wording of clinical trial regulation no 536/2014.