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 the ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP Referansedokument.

2 SCOPE

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

If Sponsor is external, e.g. a pharmaceutical company, the sponsor's SOPs can be used, provided that these are in line with national and international laws, regulations and ICH GCP.

3 RESPONSIBILITIES

Sponsor has the overall responsibility for clinical drug trial documentation and must file all required documents including any updated versions. If Sponsor delegates study archiving to a Contract Research Organisation (CRO), Sponsor is responsible for assuring that this SOP is followed.

Trial Master File (TMF) contains the essential documents to be archived by Sponsor, and these documents are owned by Sponsor. It is Sponsor's responsibility to create, store and update the TMF. These tasks can be delegated. If so, delegation of tasks shall be documented.

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 study.

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.

If the trial is a multi-centre trial involving more than one health facility / institution, the National Coordinating Investigator (NCI) 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.

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 center 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.).

If essential documents are not kept in the ISF, a note describing where they are kept must be filed, see Template 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 REK approval letter if it does not specify what was approved.

4.2 Before study start-up

Review section 4.1.

The TMF and ISF should be prepared by the PI/NCI 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 the PI / NCI
- Patient information sheet and informed consent forms (originals and revised versions)
- Example of the blank CRF
- Source Data List
- Template 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 with The Norwegian Medicines Agency (SLV), 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
- Study initiation monitoring 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 Handling 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 Randomisering blinding og avblinding.

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 Sjekkliste gjennomføring av klinisk legemiddelutprøving for sponsor, similarly in Sjekkliste gjennomføring av klinisk legemiddelutprøving for senter 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 Randomisering blinding og avblinding.

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 / PI / NCI.

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. from the pharmacy) 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 Avslutning og arkivering av kliniske legemiddelutprøvinger.

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. from the pharmacy) identifying the trial subjects should be kept separate from the collected data (CRF/eCRF).

Sponsor/PI/NCI will archive the TMF/ISF for at least 15 years after the trial is completed, in accordance with GCP and REK approval. For advanced therapy trials parts of the documentation should be stored for 30 years after the expiry date of the treatment, please refer to SOP Clinical Trials of Advanced Therapy Medicinal Products. 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/NCI shall ensure that there are procedures to protect the documents throughout the archiving period.

5 MANAGEMENT OF NON-COMPLIANCE

All non-compliance should be handled according to the procedures for handling non-compliance of the individual health facility / institution.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Forskrift om klinisk utprøving av legemidler til mennesker 2009-10-30-1321 - kap. 8
- Veiledning til forskrift av 30. oktober 2009 om klinisk utprøving av legemidler til mennesker
- ICH Guideline for Good Clinical Practice (ICH GCP) E6 (R2) - kap. 8.
- Eudralex, Volume 10, Chapter V.
- Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials
- 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 Avslutning og arkivering av kliniske legemiddelutprøvinger
- SOP Clinical Trials of Advanced Therapy Medicinal Products

7 ATTACHMENTS

- Template Trial Master File (TMF) Table of Content
- Template Trial Master File (TMF) Index Divider
- Template Investigator's Site File (ISF) Table of Content
- Template Investigator's Site File (ISF) Index Divider
- Template TMF/ISF Table of Content
- Template TMF/ISF Index Divider
- Template Location of Document if not in ISF
- Template Informed Consent Form Version Tracking Log
- Template Protocol Version Tracking Log
- Mal kontaktinformasjon studiegruppen
- Template Contact Information Study Team
- Mal møtedeltakere
- Template Meeting Participants
- Mal delegeringslogg
- Template Delegation of Tasks within the Study Team
- Mal prescreening log
- Template Prescreening Log
- Mal screening log
- Template Screening Log
- Mal deltagerliste inkluderte forsøkspersoner
- Template Identification and Enrollment Log

- Template Laboratory Sample Storage Log
- Mal kildedataliste
- Template Source Data List
- Template Training Log
- Mal innholdsfortegnelse apotekperm

8 DEFINITIONS

- Definisjoner

9 CHANGES SINCE LAST VERSION

Version 3.3. This SOP replaces SOP 2.5 version 3.2. Specific sections for different phases.