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 reference documents.

2 SCOPE

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

If the 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

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

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

The sponsor institution and the institution where each Principal Investigator 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 the validation documentation kept on file.

Investigator's Site File contains the essential documents to be archived by each Principal Investigator. The Principal Investigator at each site is responsible for creating, storing and updating the essential documents.

If the trial is a multi-centre trial involving more than one health facility / institution, the National Coordinating Investigator will manage the Trial Master File 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

The trial documentation consists of paper files and/ or electronic records. The trial documentation can be divided into a sponsor part known as "Trial Master File (TMF)", and a site-specific part known as "Investigator's Site File (ISF)". If the trial is a single-center trial, the essential documents in the Trial Master File and the Investigator's Site File may be filed together, 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.

4.1 TMF Set-up

The TMF should be prepared before the recruitment of the first trial subject.

4.2 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, note-to-file, the source data list, etc.).

The most important documents that should be filed are the following:

- Protocol and all the protocol amendments, dated and signed by the Principal Investigator / National Coordinating Investigator
- Patient information sheet and informed consent forms original and revised versions
- Example of the blank CRF
- Completed CRFs (if these are not kept in the ISF, a note to file, stating where they are kept)
- Source data / document list
- Trial team list, including the delegation log
- CV and documentation of ICH GCP-training
- Insurance certificate (Drug Liability Association, Legemiddelansvarsforeningen)
- Approvals, applications and correspondence with SLV, REK and internal approvals etc.
- IMP documentation (e.g. preparation and management of drug)
- Reference values, e.g. laboratory and technical procedures
- Reports of, serious adverse events or reactions (SAE/SUSAR), annual reports and final report
- Monitoring log and reports
- Agreements and contracts
- Relevant correspondence allowing reconstruction of important trial activities and decisions, or that contains other significant information
- Documentation of data management and statistics

Randomisation lists, unblinded adverse event data etc. 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.

The following should be filed in the ISF only:

- Identification and Enrollment log (code list)

- Signed informed consent forms.

If essential documents are not kept in the Investigator's Site File, 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, IB/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.

Table of contents templates for the Trial Master File and the Investigator's Site File for multi-centre trials, as well as a template for the combined TMF/ISF for a single centre trial, should be used.

There are other 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.

4.3 Updates

The contents of the TMF and ISF will be updated each time a change occurs in the documents on file. Any change in the documents should be traceable. For example, the TMF / ISF should be updated:

- When a trial subject is screened, screening log must be updated in the ISF.
- When a new investigator, or other person starts working on the trial, the updated delegation log and CV of the new employee will be filed in the ISF and TMF.
- When protocol amendments are submitted, relevant correspondence with the Competent Authorities (SLV) and the amended protocol, should be filed

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

4.4 Archiving of the TMF

The TMF, both electronic and paper documents, should be kept secure and with restricted access by the Sponsor / Investigator / National Coordinating Investigator.

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 be shredded at the end of the trial and not be included in the archived TMF / ISF.

Important emails should be stored with information about sender, recipient, and date.

Duplication of documentation should be avoided. Correspondence must be complete, for example it is not enough to file the Ethics Committee (EC/REK) approval letter if it does not specify what was approved.

Trial documentation can be paper only, a combination of paper and electronic documents, or only electronic. Usually the ISF will be paper-based, while the TMF can be electronic (eTMF). If using an electronic file, the system should be able to track who did what and when in the documents.

If an electronic TMF is used it should have the following properties:

- 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 the training documented and stored in eTMF

When paper documents are scanned to be stored in an eTMF, the original may be disposed after scanning, but the following requirements that 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. scan 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. The same procedure can be used for scanning of wet-ink signatures.

Sponsor / Principal Investigator / National Coordinating Investigator will archive the TMF / ISF for at least 15 years after the trial is completed, in accordance with GCP and EC 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 trial master file 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 / Principal Investigator / National Coordinating Investigator shall ensure that there are procedures to protect the documents throughout the archiving period.

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.

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 Note to File
- 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
- Mal TMF/ISF innholdsfortegnelse
- Mal TMF/ISF index skilleark
- 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 logg
- Template prescreening Log
- Mal screening logg
- 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

Definitions

9 CHANGES SINCE LAST VERSION

Version 3.2. This SOP replaces SOP 2.5 version 3.1. Translated to English. Adapted to EMA guidance. The most important additions are the sponsor institution's responsibility for archiving, the requirement for restricted access to data and the presence of superseded documents in the ISF has been added.