1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for data management in clinical trials.

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

2 SCOPE

This SOP is valid for all clinical trials sponsored by clinicians in Norwegian hospitals which are part of NorCRIN.

If the sponsor is external, e.g. a pharmaceutical company, the sponsor's SOPs will be used, provided that these are in line with national and international laws, regulations and ICH Guideline for Good Clinical Practice (ICH GCP).

3 RESPONSIBILITY

The sponsor has overall responsibility for ensuring that data management in clinical trials is carried out in compliance with national and international laws, regulations, ICH GCP and this SOP.

The sponsor's responsibilities shall be described in the quality system of the sponsor institution. Tasks can be delegated, and if so delegation of tasks should be documented.

The national coordinating investigator (NCI) for multicentre trials, or the principal investigator (PI) for single centre trials has the responsibility for ensuring that data management for a trial is carried out according to the requirements of this SOP.

The sponsor will assign data management tasks to suitably qualified and experienced personnel, who will function as a Data Managers througout the study. All staff who are involved in data management tasks (for example, database management, data verification and validation) must have necessary qualifications. A list of persons to whom tasks are assigned should be included in the Data Management Plan (DMP) or Data Management Personnel Log (DMPL).

If data management is performed by a third party vendor, in whole or part, this should be specified in a written agreement between the sponsor and the third party. The agreement will specify the tasks agreed upon to ensure compliance with the sponsor's requirements for data management handling.

4 PROCEDURES

4.1 Planning phase

4.1.1 Data Management Tasks

Data management will be carried out in accordance with the protocol and any protocol amendments approved by relevant authorities, see SOP Søknadsprosess, godkjenninger og oppstart.

Data managers should ensure that data in a clinical trial are accurate, secure, credible and ready for analysis. Data should be traceable and an audit trail should be available. Data protection considerations and IT security should be

safeguarded in all aspects of data management. An overview of data management tasks in a clinical trial is shown in the flowchart in Attachment 1.

Data management procedures should be described in a separate DMP.

4.1.2 Data Management Plan (DMP)

The data manager will prepare a DMP which will describe the overall strategy for all data management activities for the trial. The DMP should be completed before the start of the trial (first patient first visit).

The DMP will include, but not be limited to, the process and procedures for the following:

a) Electronic data management systems
b) Data Entry Application (DEA) design including:
    - CRF and patient reported outcomes (PRO)
    - Annotated CRF
    - User Acceptance testing
    - Approval
c) Randomisation, if applicable
d) Data entry
e) Data Quality Control including:
    - Data Verification
    - Data Validation
f) Reconciliation of SAEs, if applicable
g) Data from external sources
h) Coding
i) Data base lock
j) Archiving

The DMP will be reviewed and approved by the NCI/PI.

4.1.3 Case Report Form (CRF)

The CRF is a tool for data capture and reflects the protocol. The data which will be collected should be clearly stated in the protocol or other documents (eCRF specification).A description of the requirements for the drafting, the completion and corrections of the CRF can be found in SOP Case Report Form (CRF) and Patient Reported Outcome (PRO) Form Management. The source data for the trial should be defined in the protocol or Source Data List. The Source Data List may be site-specific.

4.1.4 Electronic data management systems

The system(s) and procedures used for electronic processing of clinical trial data will be described in the DMP. Electronic data processing means all processes carried out by electronic data systems in all or part of a trial.

The following specific requirements apply to the use of electronic data capture systems, but the underlying principles also apply to the treatment of paper CRFs.

The NCI/PI will:

a) Obtain documentation showing that the data processing system meets the requirements for completeness, accuracy, reliability and stability (validation).
b) Ensure that there are written procedures in place such as user guides for the systems

c) Document the training of the study personnel.
d) Audit trail – keep track of any changes to the entered data in the system, the reason for change and by whom the data is changed, and make sure the original data will not be deleted.
e) Ensure that security systems exist to prevent unauthorized access
f) Maintain a list of the people who have the authority to change the data (DMPL)
g) Ensure the adequate back-up of data
h) Safeguard the blinding procedures (if any)
i) Ensure that the data collected in the system match the protocol and paper CRF if applicable and are consistent with the source data

4.1.5 User Acceptance Testing (UAT)

After setup of the DEA, a UAT should be done to make sure the DEA fulfils the requirements of the protocol and meets the need of the study for collecting data.

An UAT is performed by entering dummy data (test data) in the DEA. Any findings made during the testing of the DEA and actions taken should be documented, see template User Acceptance Testing (UAT). When the UAT process is finalised, the DEA Approval form must be completed and signed before the study personnel can start entering real study data.

4.1.6 Data validation

Data validation is checks on the validity of the data to ensure consistency and reliability e.g. logical checks, outliers, medical review etc. Data validation procedures should be described in detail in the DMP.These procedures should be defined before the first patient is enrolled in the trial, but can be updated during the conduct of the study in the Data Management Report (DMR), see section 4.2.1.

4.2 Conduct phase

4.2.1 Data Management Report (DMR)

Any deviations from the finalised DMP and other data management tasks performed during the study that should be documented will be described in the Data Management Report.

4.2.2 Data verification and data validation during the study

Data verification is the process of comparing data in two different data sets e.g. paper CRF and the eCRF, or electronic files and the eCRF. Source data verification (SDV) is a special kind of data verification where data in the CRF are compared with the source documentation.

Ongoing data verification and validation will be carried out as described in the DMP. Possible errors detected during verification or validation of data will require entry of correct data and this process continues until database lock.

A final validation of the data will be carried out once all data have been entered (or imported) as described in the DMP to ensure the trial data are valid and reliable.

4.2.3 Coding

Project specific coding procedure should be defined as early as possible and documented in the DMP. The DMP should cover which clinical terms are to be coded and the dictionaries to use for the coding. The most used coding dictionaries are MedDRA and CTCAE for Adverse Events, ATC for drugs and ICD-10 for diagnosis.

4.2.4 Serious Adverse Event (SAE) reconciliation

Applies when SAEs are reported to an external database (e.g. safety reporting to pharmaceutical companies or when the SAEs are kept in another database than the eCRF). The variables to be reconciled and the requirement for exact match/equivalence/medically consistency should be defined in the DMP, together with timelines for when SAE reconciliation should take place during the study. The last reconciliation will be performed immediately before database lock. The result from the SAE reconciliation process will be documented in the DMR during the study.

4.2.5 Data monitoring committee (DMC)

Whether there is a DMC in the study should be described in the protocol.

The NCI/PI will ensure that there is charter (see the Template DMC Charter) for the work of the committee. The charter should describe in detail which data are to be delivered and by whom, and the appropriate format (tables, listings etc.) for DMC meetings, and if the data should be verified/validated/coded before the meetings. If not stated in the DMC charter, timelines for assuring delivery of data in due time should be discussed with the NCI/PI. The data management deliveries and timelines should be described in the DMP.

4.2.6 Changes to the DEA

Changes to the DEA may be required from time to time due to e.g. protocol amendments or data requirements. Substantial protocol amendments need approval from the Norwegian Medicines Agency (SLV) and/or Regional Committees for Medical and Health Ethics (REK), or other relevant authorities abroad, before the changes can be made to the DEA, see SOP Protokolltillegg og endringer etter studiestart.

The data manager should do a risk assessment and consider the potential impact of the foreseen changes to the DEA and the already entered data in the database. The impact of the changes must be discussed and approved by the NCI/PI before any changes are done to the DEA. It is recommended to discuss the changes with the statistican.

Any changes done to the DEA during the study should be documented in a DEA Change Log and described in the data management report (DMR) at the end of the study. The CRF, the DEA and the data records should have version control corresponding to the DEA Change Log.

4.2.7 Database lock

After data collection is finalised and data validation processes defined in the DMP have been carried out (data validated, queries resolved, final coding and possible SAE reconciliation has been performed) a data closure meeting should be arranged.

Listings of all study subjects and their allocation to the different populations according to the protocol / Statistical Analysis Plan (SAP) (e.g. intention-to-treat (ITT), per protocol (PP) and safety) must be finalised before database lock. When the database is locked all write privileges must be removed from all users. The database lock will be documented on the Database Lock Form. The datasets will be exported and made available for the analyses defined in the SAP.

4.3 Close out

4.3.1 Tables, listings and figures (TLFs)

The TLFs defined in the SAP will be prepared either by the data manager or the statistician and the NCI/PI will ensure the quality checks are carried out on all the TLFs by a review of a sample of the data and comparisons with raw data listings.

4.3.2 Database Unlock

If data errors are detected which either:

a) Have a significant impact on the statistical outcome of the analysis
b) Affects the safety profile of the investigational product

The database may be unlocked to correct the errors after a formal written request from both the data manager and biostatistician is approved by NCI/PI and should be documented on Database Unlock Form.

The reason for unlock and the data which will be corrected must be clearly stated on the request. Once the approval is granted the data manager will grant write privileges to a designated person/persons (e.g. investigator/study nurse), who will enter the corrections. Once the corrections have been made the data manager will remove the write privileges to the database and the database will be relocked. The correction of the re-locked database will be confirmed on Database Relock Form.

The changed datasets will be exported and made available for analysis.

4.3.3 Data management report

The DMR should be finalized when the close out is completed for the study.

4.3.4 Storage / archiving of data and code lists

The completed CRFs and source documents should be kept secure and access restricted to authorised persons during the conduct phase of the trial. The completed CRFs should be kept separate from the randomization code list.

Electronic data must be stored securely and in compliance with REKs requirements and the Norwegian Directorate of Health' guideline: "Privacy and information security in the research projects within the health and care sector".

Procedures for the export of data (e.g. in multi-centre trials) should be described in the DMP and should be performed according to the current regulatory requirements. The export of human biological material to other countries is governed by specific regulations (refer to Norwegian Health Research Act § 29).

At the end of the trial, the data and essential documents, including any code list and audit trails, must be archived. For further description of the requirements for archiving data and essential trial documents refer to the SOP Study Files and SOP Avslutning og arkivering av kliniske legemiddelutprøvinger

5 NON-CONFORMANCE MANAGEMENT

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

6 REFERENCES

6.1 External References

- Lov om medisinsk og helsefaglig forskning (helseforskningsloven) § § 7, 29.
- ICH Guideline for Good Clinical Practice E6 (R2).: section 2.10, 2.11, 2.13, 4.9, 5.5, 5.15

- Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials.
- Health's supervisor "Privacy and information security in the research projects within the health and care sector" (NORMEN)
- ECRIN Data center certification standards for enhanced quality
- ICH E9 Statistical Principles for Clinical Trials
- EMA Guideline on Data Monitoring Committees

6.2 Internal References

- SOP Case Report Form (CRF) and Patient Reported Outcome (PRO) Form Management
- SOP Protocol
- SOP Randomisering, blinding og avblinding
- SOP Study Files
- SOP Avslutning og arkivering av kliniske legemiddelutprøvinger

7 ATTACHMENTS

- Template Data Management Plan
- Template Data Management Report
- Template DEA Approval Form
- Template Database Lock Form
- Template Database Unlock Form
- Template Database Relock Form
- Template Data Management Personnel Log
- Template User Acceptance Testing (UAT)
- Template DEA Change Log
- Template Source Data List
- Template DMC Charter

8 DEFINITIONS

- Definisjoner

9 CHANGES SINCE LAST VERSION

SOP version 3.1. This SOP replaces SOP No. 2.6 version No. 3.0. Major changes are specific sections for different phases and the addition of some more templates.

10 ATTACHMENT 1