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, specified in the Reference document.

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 and ICH GCP and this SOP.

The sponsor's responsibilities shall be described in the governing documents (quality system) of the individual health facility / the individual institution. Tasks can be delegated. The delegation of tasks shall be documented.

The national coordinating investigator (for multi-centre trials) or the principal investigator (for single-centre trials)(NCI/PI) 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 data managers. All staff who are involved in the data handing (for example, database management, verifying and validating data) must possess the necessary qualifications for the task. A list of the persons to whom tasks are assigned should be included in the data management plan, or other document, for example, written agreements.

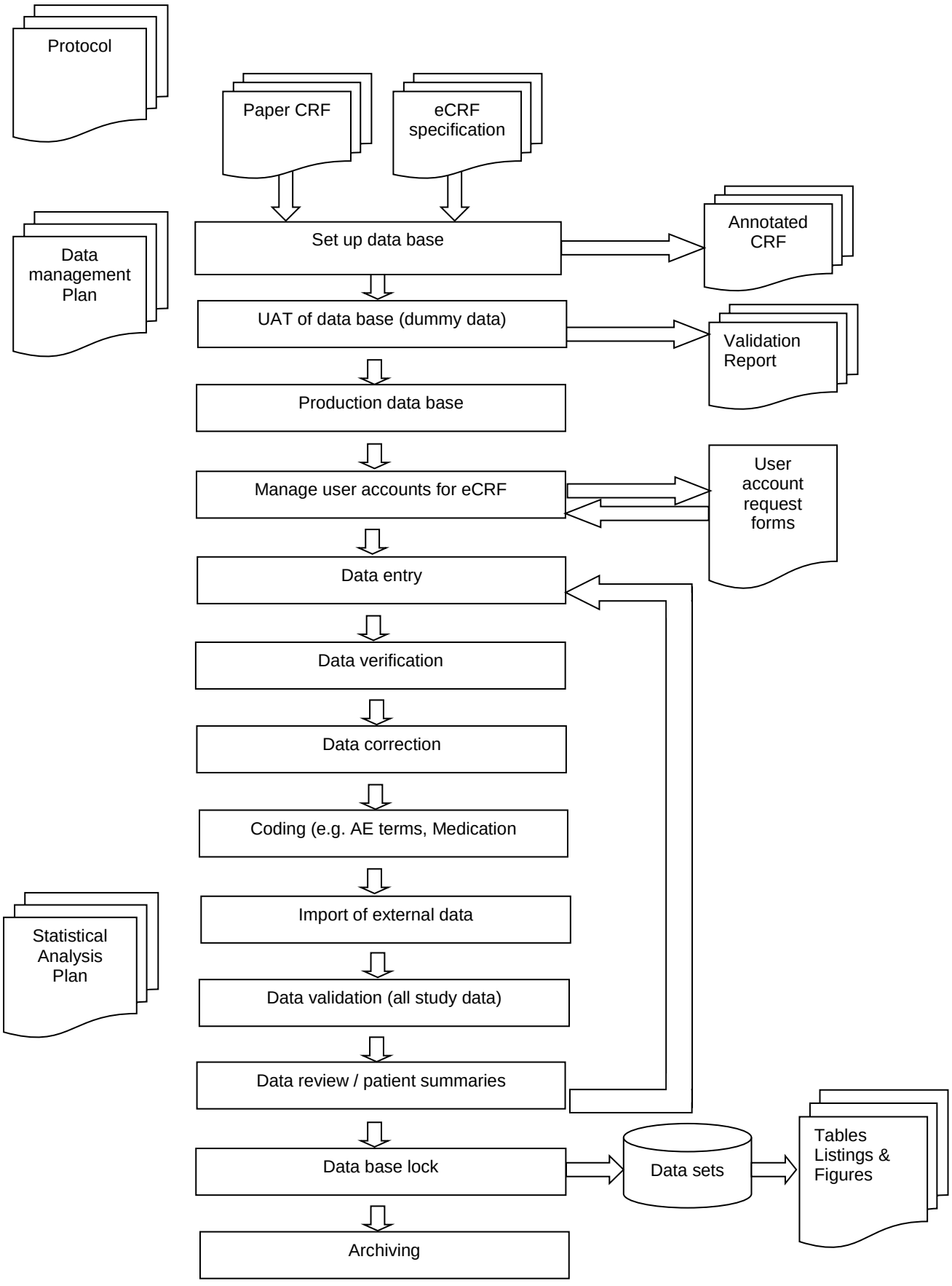
If the data management is performed by a third party vendor, in whole or part, this shall be specified in the written agreement between the sponsor and the third party. The agreement will specify activities to ensure compliance with the sponsor's requirements for quality and security in data management.

4 PROCEDURES

4.1 Data Management Tasks

Data managers should ensure that the data in a clinical trial is accurate, secure, credible and ready for analysis. Data should be traceable and an audit trail should be available. Privacy considerations and IT security should be safeguarded in all aspects of data management.

An overview of data management in a clinical trial is shown in the flowchart below.


Protocol
Paper CRF
eCRF specification
Data management Plan
Set up data base
Annotated CRF
UAT of data base (dummy data)
Validation Report
Production data base
Manage user accounts for eCRF
User account request forms
Data entry
Data verification
Data correction
Coding (e.g. AE terms, Medication
Statistical Analysis Plan
Import of external data
Data validation (all study data)
Data review / patient summaries
Data base lock
Data sets
Tables Listings & Figures
Archiving

Data verification is the process of comparison between data in two different data sources e.g. paper CRF and database or electronic file and database

Data validation is a check on the validity of the data e.g. logical checks, outliers, medical review, etc.

Discrepancies detected during verification or validation of data will require entry of correct data and this process continues until database lock.

Data management procedures can be described in the protocol or in a separate data management plan. See attached template for the data management plan.

4.1.1 Data Management Plan (DMP)

The data manager will prepare a data management plan (using the DMP template) which will describe the overall strategy for all data management activities for the trial.

Work on the data management plan should start at the time of protocol writing and be completed before the start of the trial (first patient first visit).

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

a) Data base design and approval
b) CRF and patient questionnaires, patient reported outcomes (PRO)
c) Data base set-up
d) User acceptance testing of data entry application and data base (including electronic CRF and electronic PRO)
e) Data entry
f) Data quality control
g) Data verification
h) Data correction (including query management)
i) Coding
j) Import of external data
k) Data validation (including SAE reconciliation)
l) Data base locking
m) Archiving

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

4.1.2 Data management report

Any changes to the DMP after approval will be reflected in the data management report (DMR). The data management report template should be used when writing the DMR.

4.1.3 Case Report Form (CRF)

Case Report Form (CRF) is a tool for data capture and reflects the protocol. A description of the requirements for the drafting, the completion and corrections of the CRF can be found in SOP Preparation and completion of Case Report Form (CRF) and patient reported outcome (PRO) forms.

4.1.4 Recording and Managing the Data

The data (variables and endpoints etc.) which will be collected and the methods to be used to accurately measure these should be clearly stated in the protocol or other document. See SOP Protocol.

Data management will be carried out in accordance with the protocol and any protocol amendment that has received approval from the REK (Regional Committees for medical and health research ethics) and the Norwegian Medicines Agency and other relevant authorities abroad.

The source data for the trial should be defined in the protocol or other document [kildedataliste]. The source data list may be site-specific.

4.2 Quality assurance and quality control

NCI/PI is responsible for ensuring that there are procedures to ensure the quality at every step of the data management in the trial. Quality control procedures will be described in the protocol and defined in detail in the data management plan. These procedures should be defined before the first patient is enrolled in the trial.

Ongoing data verification and validation will be carried out as described in the data management plan.

A final validation of the data will be carried once all data has been entered (or imported) as described in the data management plan to ensure the validity and reliability of the trial data.

4.3 Electronic data management systems

The system and procedures for the use of electronic processing of clinical trial data will be documented 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 such as user guides for the use of these systems
c) Verify that changes to the data will not cause the original or previously entered data to be deleted (audit trail)
d) Ensure that security systems exist to prevent unauthorized access
e) Maintain a list of the people who have the authority to change the data.
f) Ensure the adequate back-up of data
g) Safeguard the blinding procedures (if any)
h) Ensure that the data collected in the system match the protocol and paper case report form (CRF) if applicable and are consistent with the source data

4.4 Database lock

After data collection is finalised and quality control processes defined in the DPM have been carried out (that is the data is validated) the database must be locked (that is all write privileges will be removed from all users) by the computer system administrator. The database lock will be documented on Database Lock form.

The datasets will be exported and made available for the analyses defined in the SAP.

4.5 Tables listings and figures (TLFs)

The Tables, listings and figures defined in the SAP will be prepared and the NCI/PI will ensure the QC checks are carried out on all the tables, listings and figures by a review of a sample of the data and comparisons with raw data listings.

4.6 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.

The reason for unlock and the data which will be corrected must be clearly stated on the request. Once the approval is granted the computer systems administrator will grant write privileges to the data manager, who will enter the corrections. Once the corrections have been made the computer systems administrator will remove the write privileges. The database relock will be documented on Database Lock form.

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

4.7 Storage/archiving of data and code lists

The completed CRF and source documents should be kept secure and access restricted to authorised persons during the active phase of the trial. The completed CRF 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 data to other countries is governed by specific regulations (refer to Norwegian Health Research Act § § 29 and 37).

At the conclusion of the trial, the data and essential documents, including any code list, shall be archived. For further description of the requirements for archiving data and essential trial documents refer to the SOP Studiearkiv and SOP Avslutning og arkivering av kliniske legemiddelutprøvinger

4.8 Data monitoring committee

The need for a data-monitoring committee (DMC) will be considered for each trial. The task of the DMC is to review the safety data and critical data at specified intervals and to determine whether or not to continue, modify, or stop the trial.

The NCI/PI will ensure that there is clear charter (see the Template DMC charter) and guidelines for the work of the committee. Minutes will be kept of the committee's meetings.

5 NON-CONFORMANCE MANAGEMENT

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

- Act on medical and health research (the Health Research Act) § § 7, 29 and 37.
- Integrated Addendum To ICH E6(R2): Guideline for Good Clinical Practice
  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 PPI No 211738 ECRIN Standard requirements for GCP-compliant data management in multinational trials
- ICH E9 Statistical Principles for Clinical Trials
- EMA Guideline on Data Monitoring Committees

6.2 Internal References

- SOP Utarbeidelse og utfylling av Case Report Form (CRF) og pasientutfylte skjema

- SOP Protokoll
- SOP Randomisering, blinding og avblinding
- SOP Studiearkiv
- SOP Avslutning og arkivering av kliniske legemiddelutprøvinger

7 ATTACHMENTS

- Template Data Management Plan
- Template Data Management Report
- Template Database Lock Form
- Template Database Unlock Form
- Mal Kildedataliste
- Template DMC charter

8 DEFINITIONS

Definitions

9 CHANGES SINCE LAST VERSION

SOP version 3.0. This SOP replaces SOP No. 2.6 version nr.2.0 and is written in English. Major changes.