1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for writing, reviewing and approving clinical drug trial protocols.

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 drug trials sponsored by institutions that have implemented the NorCRIN SOPs.

If the sponsor is external to the institution, e,g. a pharmaceutical company, the sponsor's SOPs will be used, provided they are in line with national and international laws, regulations and ICH GCP.

3 RESPONSIBILITIES

The sponsor has overall responsibility for ensuring that clinical drug trial protocols are managed in compliance with 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. All staff who are involved in writing, reviewing and approving clinical drug trial protocols, must possess the necessary qualifications for the task. The delegation of tasks shall be documented, for example in written agreements.

The Principal Investigator in a single centre study/National Coordinating Investigator in a multicentre study (PI/NCI) has the responsibility for ensuring that the writing, reviewing and approving protocols is in compliance with this SOP. In depth information of the procedures are described in section 4.

If tasks are 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 that the sponsor's requirements for quality are complied with.

4 PROCEDURES

The PI/NCI will ensure that the protocol describes the objective(s), design, methodology, statistical considerations, organisation and estimated time frames for the trial. The protocol should also give the background and rationale for the trial and should be designed to provide answers to a specific research question.

The protocol provides the basis for an application for approval of the clinical drug trial by the Competent Authority and Ethics Committee(s). A summary of the protocol can also be the basis for an application for funding of the project.

4.1 RISK ASSESSMENT

During protocol development and in order to comply with GCP requirements, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results. The sponsor should identify and evaluate risks to the critical trial processes and data. Pre-defined quality tolerance limits should also be established e.g. a drop-out rate of 5% is acceptable but if it becomes higher the PI/NCI will implement measures in other to reduce drop-out such as inform the patient in a better way. Appropriate risk reduction activities may be described in the protocol or documented in the risk assessment. The template Risikovurdering can be used to document the risk assessment and the action which will be taken to mitigate the risks.

4.2 PREPARATION OF THE DRAFT PROTOCOL

The requirements for the content in a protocol are specified in chapter 6 of the ICH guideline for GCP.

The following requirements should also be followed:

- Forskrift om klinisk utprøving av legemidler til mennesker (FOR-2009-10-30-1321) and key steps listed in veiledningen to forskriften.
- Requirements of Helseforskningsloven
- Forskrift om organisering av medisinsk og helsefaglig forskning § 8.

The PI/NCI should consider establishing committees to oversee specific aspects of the trial, e.g.:

- An executive committee or trial management committee
- A steering committee
- An endpoints adjudication committee
- A data monitoring committee (DMC)

A description of the different kinds of committees can be found here.

When a DMC is involved in a trial the role of the DMC must be described in the protocol. The published EMA guideline on DMC should be followed and a DMC charter must be written.

The protocol should preferably be written in English. A protocol template is available on Transcelerate's website, see guidance for use.

The PI/NCI should also consult the European Medicines Agency guidance for various types of studies, various therapeutic areas and biostatistics issues.

Statistical methods and how the data will be analysed must be outlined in the protocol. To maintain transparency, the description should be sufficiently detailed to allow a complete reproduction of the following results. Due to the complexity of modern statistical analyses, a separate statistical analysis plan (SAP) is highly recommended. The SAP should prespecify all statistical analyses, and must be finalised prior to database lock. Any analyses not specified in the protocol or SAP should be regarded as post-hoc analyses. A SAP template is available on Transcelerate's website, see guidance for use.

Protocols must have a version number and date. When updating a protocol the version number and date must be updated. The updated protocol should have a document history with previous versions and version dates.

4.3 REVIEW AND APPROVAL

It is recommended that PI/NCI asks other persons who will be involved in the trial to review the protocol prior to submission to any internal approval, the Competent Authority and Ethics Committee(s). For example, other investigators, trial personnel, laboratory personnel, pharmacist etc. that will perform trial tasks, often have experience and can provide useful input on how the trial procedures should be implemented. In addition, the PI/NCI should, as early as possible, contact research support units and statisticians who can help with the choice of statistical methods and provide statistical input (power calculation, sample size, etc.).

The protocol shall be signed by the sponsor representative as described in the institution's procedure for Roles and responsibilities (Roller og ansvar i kliniske legemiddelutprøvinger og utprøving av medisinsk utstyr).

More details on the preparation of applications to the Competent Authority and Ethics Committee(s) can be found in the SOP Søknadsprosess, godkjenninger og oppstart.

Changes to an approved protocol and possible need for reapproval is described in SOP Protokolltillegg og endringer etter studiestart.

4.4 DOCUMENTATION

All approved versions of the protocol and correspondence with the Competent Authority and Ethics Committee(s), will be filed in trial master file; see SOP Study Files. It is recommended that the Protocol Version Tracking Log Template is used to keep a record of protocol versions.

5 NON-COMPLIANCE MANAGEMENT

All non-compliance should be handled according to the procedures for handling non-compliance of the individual health facility / institution and SOP Issue Management (link).

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Forskrift om klinisk utprøving av legemidler til mennesker 2009-10-30-1321
- Forskrift om organisering av medisinsk og helsefaglig forskning, § 8
- Veiledning til forskrift av 30. oktober 2009 om klinisk utprøving av legemidler til mennesker, kap. 4
- ICH E6 GCP, section 6.
- ICH E9 Statistical Principles for Clinical Trials.
- EMA Guideline on Data Monitoring Committees
- EMA Scientific guidelines

6.2 INTERNAL REFERENCES

- SOP Søknadsprosess, godkjenninger og oppstart
- SOP Protokolltillegg og endringer etter studiestart
- SOP Study Files
- SOP Note to File

7 ATTACHMENTS

- Guidance for access to Transcelerate's protocol and SAP templates
- Sjekkliste innhold protokoll
- Template Protocol Version Tracking Log
- Mal risikovurdering
- Template DMC Charter

8 DEFINITIONS

- Definitions

9 CHANGES SINCE LAST VERSION

This SOP will replace SOP No. 2.1 version nr. 3.0. Changes are translation into English, inclusion of risk assessment, shorten information about changes to an approved protocol. Links are changed to reflect that the Transcelerate protocol template and SAP template now replaced former templates.