1 PURPOSE

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe sponsor's tasks and responsibilities for monitoring in clinical trials.

The SOP should ensure that national and international laws and regulations and ICH Guideline for Good Clinical Practice (ICH-GCP) specified in the SOP Referansedokument are followed.

The aim of monitoring is to verify that:

- The rights, well-being and integrity of the trial participants are safeguarded.
- The collected data is correct, complete and in accordance with source data.
- The trial is conducted according to a valid protocol, regulations and ICH-GCP.

2 SCOPE

The SOP is valid for all clinical drug trials in which the sponsor has implemented the NorCRIN SOPs.

3 RESPONSIBILITIES

Sponsor has an overall responsibility to ensure the clinical drug trial is monitored.

Sponsor's responsibilities shall be described in the quality system of the sponsor institution. Tasks are delegated according to SOP Roles and Responsibilities in clinical trials implemented in the institution.

Principal Investigator in a single center trial or the National Coordinating Investigator in a multicenter trial (PI/NCI) should appoint a qualified monitor and write a risk-based monitoring plan that the monitor should follow.

The Principal Investigator (PI) at each site is responsible for facilitating monitoring and follow up on pending action items.

4 APPROACH

4.1 DUTIES OF PI/NCI

PI/NCI should appoint a monitor and have a trial monitoring agreement in place. Clinical Trials Units (CTU) at the university hospitals will be able to provide monitoring or inform about other hospitals or Contract Research Organisations (CROs) that do.

It is recommended that the monitor is independent, i.e. that the monitor is not a direct report, a close colleague or in any other way has a personal relationship to the PI/NCI or to the site staff.

PI/NCI should ensure that the monitor has sufficient scientific and/or clinical knowledge to monitor the trial in an adequate way. The qualifications of the monitor should be documented in the Trial Master File (TMF).

PI/NCI should define the level and degree of monitoring. Monitoring will usually be performed at the site before, during and after the conduct of the trial. Based on the risk assessment described in the SOP Quality and Risk Management, a Monitoring Plan should be written. This may be done in collaboration with the monitor.

The sponsor should have a plan prior to initiation of the trial for how deviations should be recorded, handled and reported in the study, see SOP Protocol Deviation Handling.

The tasks described above can be delegated to the PI/NCI.

The monitor will send a report from each monitoring visit to the PI/NCI within 14 calendar days. PI/NCI should review and sign the monitoring reports within 14 calendar days and return a signed copy to the monitor.

4.2 PRINCIPAL INVESTIGATOR'S DUTIES

The PI must be available and ensure that facilities required for monitoring are in place. Facilities include an office place, access to study documents, source data and other relevant documentation and equipment to be monitored.

The PI should give the monitor access to source data in the medical records in accordance with the hospital's procedures. The monitor should preferably get their own log-in credentials to the medical records (read-only access) if possible. If this cannot be granted, the investigator or study nurse has either to log in and sit together with the monitor while source data verification (SDV) is performed or print out all relevant medical notes.

The PI is responsible for making corrections and follow-up on deviations and actions identified at the monitoring visit. The actions to be followed up will be listed in an attachment to the report and forwarded to the PI and other relevant site staff by the monitor, within 14 calendar days after a monitoring visit. The PI or designated site staff should complete the tasks within the timeframe given and return a signed copy of the attachment to the monitor.

Handling of deviations is described in Protocol Deviation Handling Plan.

4.3 INITIATION VISIT

An initiation visit should be performed by the monitor at each study site before the study is initiated to ensure all required documents and IMP are in place. The initiation visit may be combined with the start-up meeting, see SOP Søknadsprosess, godkjenninger og oppstart and Mal Agenda oppstartsmøte.

The monitor will decide whether the site is ready to start enrolment or not based on issues identified. Examples of major issues are; pending approvals or agreements, missing/incomplete delegation log, insurance certificate, source data list, study drug or training of study personnel. The PI has to confirm that these issues are resolved before "green light" for enrolment is given by monitor.

4.4 MONITORING VISIT

The Monitoring Plan should define when the first monitoring visit is to take place and the frequency of the subsequent visits. Usually the first visit will take place shortly after inclusion of the first trial participants.

The Monitoring Plan should also clearly define focus and tasks at the monitoring visits.

The risk evaluation of the study should be reviewed regularly throughout the study based on e.g.:

- Feedback from the monitor or data manager
- Serious Adverse Event (SAE) reporting leading to change in the risk-benefit ratio
- Findings or publications from relevant clinical studies
- Report from Data Monitoring Committee (DMC)
- Findings or publications from relevant preclinical studies

Changes in risk evaluation may require a change in the monitoring plan for the entire study or for specific sites.

4.5 CLOSE-OUT VISIT

A close-out visit should be performed at each site after the last patient last visit. Deviations from this may be the case in studies with a long survival follow-up period, and should be explained in the Monitoring Plan.

4.6 OFF-SITE MONITORING

Off-site monitoring is defined as monitoring of a site by phone or videoconference. The frequency of off-site monitoring and items to be checked and discussed should be described in the monitoring plan. If a videoconference is going to be used and the monitoring plan requires verifying of sensitive information, for instance signed informed consent forms or source data with personal information, a secure solution approved by the site institution is required.

Off-site monitoring may be undertaken for a variety of purposes:

- to educate staff about the trial and review understanding of the protocol and trial procedures
- to verify that the site has access to the necessary documentation to conduct the trial appropriately
- to ensure adequate resources and facilities are available
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms, patient eligibility and logs
- to identify problems and suggest solutions
- to maintain good relations with the investigator and trial personnel

Off-site monitoring can be time efficient and reduce costs, as no travel is required. However, off-site monitoring should primarily be considered for the following type of studies:

- simpler studies with low risk
- studies with many sites, but few subjects
- studies with site staff familiar with doing clinical trials and familiar with the study drug

Off-site monitoring is not recommended for the following type of studies:

- - studies requiring monitoring of the pharmacy and/or biobank and/or other facilities at site
- - studies requiring extensive source data verification

The decision to perform off-site monitoring in a study should be risk based and made by the PI/NCI.

Off-site monitoring requires certain facilities at each site, such as

- study staff able to prepare for the monitoring
- study staff able to spend time during the whole telephone- or videoconference
- eligible meeting room facilities with conference equipment, especially if videoconference is going to be used

A feasible length of an off-site monitoring visit is from one to three hours. If the items to be checked and monitored are extensive and the visit is expected to last for more than three hours, on-site monitoring should be considered.

Off-site monitoring can be combined with on-site monitoring in a study or it can be the primary way of monitoring a study. However, there should always be an opportunity to perform visits planned as off-site visits in the monitoring plan as an on-site visit, if required.

Reasons for performing on-site monitoring instead off-site monitoring can be:

- unexperienced site staff
- need of additional training and advising
- misconduct
- protocol deviations
- safety issues or other issues discovered during an off-site monitoring visit

4.7 MONITORING OF BIOBANK

In clinical trials samples of biological material may be stored in freezers/refrigerators which are not a part of an organized biobank. Based on the risk assessment it may be necessary to monitor the biobank.

4.8 MONITORING OF BLINDED STUDIES WITH UNBLINDED PERSONNEL

In blinded clinical trials where un-blinded site personnel, e.g. a pharmacist or a study nurse preparing the treatment, work together with personnel that should be kept blinded, e.g. the treating physician or evaluator, it is important to have procedures in place to ensure that no un-blinded information is disclosed to the blinded site staff. In these studies, it is required to have two monitors, one blinded monitor monitoring all the study data and one un-blinded monitor reviewing the IMP-logs and other un-blinded information.

4.9 CENTRALIZED MONITORING

Centralized monitoring (CM) is checks performed on an aggregated level either per site or between sites. CM is performed with the intention to check that the collected data indicate that all sites interpret the protocol the same way and use the eCRF in a consistent manner, and that no unintended center effects make drawing conclusions from the study dubious. CM is performed with the intention to improve quality and not to evaluate the safety or efficacy of the treatment and may impact on-site monitoring.

CM covers both metrics (enrolment speed, time to CRF completion, etc.) and critical data evaluation.

The strategy for monitoring, including the use of CM, will be described in a monitoring plan. A description of the CM, including data validation, will be detailed in the Data Management Plan.

4.10 DOCUMENTATION

All monitoring reports should be filed in the TMF/ISF.

5 HANDLING OF DEVIATIONS

Documentation of non-compliance in the individual study should be handled according to SOP Protocol Deviation Handling and according to the procedures for handling non-compliance of the individual health facility / institution.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Lov om medisinsk og helsefaglig forskning LOV-2008-06-20-44 (helseforskningsloven)
- Lov om legemidler m.v. LOV-1992-12-04-132 (legemiddelloven)
- Forskrift om klinisk utprøving av legemidler til mennesker FOR-2009-10-30-1321 (KLUT-forskrift)
- Forskrift om legemidler FOR-2009-12-18-1839 (legemiddelforskriften)
- EUs Clinical Trial Directive, 2001/20/EC- EU-direktivet for kliniske legemiddelutprøvinger

- EUs Clinical Trial Directive 2005/28/EC – EU-direktivet for ICH GCP
- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) kap. 5.18
- Best practices for repositories: collection, storage, retrieval, and distribution of biological materials for research. Biopreserv Biobank 2012; 10: L2.300 Protection from Research Risks.

6.2 INTERNAL REFERENCES

- SOP Protocol Deviation Handling
- SOP Quality and Risk Management

7 ATTACHMENTS

- Template Protocol Deviation Handling Plan
- Mal Initieringsrapport monitorering
- Template Study Initiating Monitoring Report
- Mal Monitoreringsrapport
- Template Monitorering Report
- Mal Avslutningsrapport monitorering
- Template Final Trial Close-out Monitorering Report
- Mal Monitorering av forskningsbiobank
- Template Biobank Monitoring Report
- Template Query List
- Template Trial Handover Procedure and Checklist

8 DEFINITIONS

- Definisjoner

9 CHANGES FROM PREVIOUS VERSION

Version 3.2 replaces version 3.1. Divided SOP monitoring into one for sponsors and principal investigators and one for monitors. Included sec 4.8 about blinded trials.