1 PURPOSE

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

The purpose of monitoring is to verify that:

- The rights, safety and well-being of subjects are protected
- The reported trial data are reliable and robust (accurate, complete, and verifiable from source documents).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)

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

2 SCOPE

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

3 RESPONSIBILITIES

The sponsor has overall responsibility for ensuring that clinical trials are monitored.

Tasks can be delegated. The delegation of tasks shall be documented, for example in written agreements.

All staff who are involved in monitoring of clinical trials must possess the necessary qualifications for the task.

If monitoring 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 that the sponsor's requirements for quality are fulfilled.

3.1 Sponsor

The sponsor's responsibilities shall be described in the governing documents (quality system) of the individual institution.

3.2 Coordinating Investigator

The coordinating investigator has the responsibility for ensuring that monitoring is carried out according to the requirements of this SOP.

The coordinating investigator will assign monitoring tasks to qualified monitors.

3.3 Principal Investigators

Principal investigators should be available for discussions with monitor and facilitate monitoring visits by providing office space, access to study documents, source data and other relevant documents and equipment required for the trial.

Principal investigators are responsible for making corrections and following up on deviations and actions identified in the monitoring report, or in other documents including, but not limited to, notes to file.

4 PROCEDURES

4.1 Selection and qualifications of monitors

The sponsor shall appoint monitors with suitable scientific and / or clinical knowledge in order to monitor the study satisfactorily.

Monitor qualifications (CV) must be documented in TMF.

The monitor should be independent, i.e. the monitor must not be a direct report, a close colleague or in any other way have a close relationship to the site staff.

If the monitor is not employed at the sponsor institution, the sponsor should ensure a Data Processing Agreement is signed.

4.2 Extent and nature of monitoring

Site monitoring should be done before, during and after the trial. For some trials centralised monitoring with reduced numbers of on-site visits may be appropriate.

The extent and nature of the monitoring shall be determined by the coordinating investigator on the basis of a risk assessment (see SOP Quality and Risk Management with attachments) that takes into consideration all characteristics of the clinical trial, including but not limited to the following:

- whether the clinical trial is a low-intervention clinical trial
- the objective and methodology of the clinical trial
- the degree of deviation of the intervention from normal clinical practice

4.3 Monitoring Plan

The coordinating investigator should in collaboration with the monitor prepare the monitoring plan, which will include procedures to mitigate any risks (see SOP Quality and Risk Management with attachments), before the first monitoring visit takes place.

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

The Monitoring Plan should clearly define what to monitor during monitoring visits.

If centralised monitoring will be performed, the process will be described in the monitoring plan and the Data Management Plan.

The coordinating investigator can amend the monitoring plan based on, for example:

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

4.4 Monitoring

Monitors should be familiar with the investigational product, trial protocol, patient information and consent form, ICH GCP and applicable laws and regulations.

Monitors shall follow the procedures described in the monitoring plan.

The principal investigator should give the monitor access to source data in the medical records in accordance with the hospital's procedures. The monitor should be given 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 to log-in and sit together with the monitor when doing source data verification or print out all relevant medical notes to allow source document verification.

After each on-site monitoring visit, the monitor should complete a visit report. The report should be completed and forwarded to the sponsor/ coordinating investigator as a pdf-document within 14 calendar days. Attachment 1 with the action list for the site should be attached. At the same time, the action list should be sent to the site, as a pdf-document. The complete report can be sent to the site, as well, but this is not mandatory, except for the Initiation Visit Report, which should be filed in the investigator's site file (GCP requirement).

The sponsor/ coordinating investigator (or the coordinating investigator designated representative) will review monitoring reports, to ensure that any sponsor issues reported by the monitor are followed-up, and site issues noted and signs the report within 14 calendar days.

Sponsor/ coordinating investigator should review and sign the monitoring reports within 14 and return a signed copy to the monitor.

The actions to be followed up will be listed in an attachment to the report and forwarded to the Principal Investigator and other relevant site staff by the monitor within 14 calendar days after a monitoring visit. The Principal Investigator or designated site staff should complete the tasks within the timeframe given and then return a signed copy of the attachment to the monitor.

Issue management include deviation management will be handle as described in the SOP Issue Management.

4.4.1 Initiation Visit

Initiation visits must take place at each trial site before the start of the trial (that is before investigational product is sent to the site, or before the first patient is recruited).

Monitors will contact the principal investigators at each trial site to arrange the time and place for initiation visits. Monitors will also visit other facilities involved in the trial (e.g. pharmacies, laboratories etc.), as necessary.

During the initiation visit the monitor should use the checklist in the Trial Initiation Report.

The initiation visit report will be written by the monitor and will be signed by the monitor and sponsor/ coordinating investigator representative.

The monitor will decide whether the site is ready to start enrolment or not, based on the issues found. 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 Principal Investigator must confirm that all major issues are resolved before the eCRF is made available to the site and enrolment can start. In studies with eCRF, the monitor will forward a completed and signed Green Light Document to the data manager, with copy to Principal Investigator and coordinating investigator, to confirm the site can be given access to the eCRF and start enrolling.

4.4.2 Routine Monitoring Visits

The first routine monitoring visit is usually carried out at each trial site as early as possible after inclusion of the first subject. Other monitoring visits will be carried out in compliance with the monitoring plan.

Monitors shall inform the principal investigators of any CRF entry error, omission, or illegibility.

The monitor should check that corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by / be attributable to the investigator or by a member of the investigator's trial staff authorised to make CRF changes.

Monitor cannot make any corrections or changes to the CRF data.

In case deviations are not entered directly into an eCRF as queries, the deviations should be listed in the report or on a separate list (query list).

The routine Monitoring Report will be written and signed by the monitor, principal investigator and sponsor representative (coordinating investigator or other). The original signed report will be filed in the sponsor's TMF and a copy will be filed in the investigator's site file.

4.4.3 Close-Out Visit

Trial close-out visits should be done at each trial site at the end of the trial.

During the close-out visit the monitor will use the checklist in Close-out Monitoring Report.

The close-out visit report will be written and signed by the monitor, and sponsor/ coordinating investigator representative). The attachment with any pending queries will be signed by the principal investigator or designee. The original signed report will be filed in the sponsor's TMF and a copy will be filed in the investigator's site file.

Sites which never received investigational product can be closed without an on-site visit.

4.5 Biobank Monitoring

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

In case the Monitoring Plan requires monitoring of a biobank, the monitor should complete the Biobank Monitoring Report.

4.6 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 for study data monitoring and one un-blinded monitor reviewing the IMP-logs and other un-blinded information.

4.7 Monitor Handover Checklist

If there is a change in monitor for a study at a site, the outgoing monitor should inform the new monitor about the monitoring status of the site using a checklist. A copy of the handover checklist should be filed as part of the new monitor's training documentation, together with the monitor's CV in the TMF, to document monitor's qualifications.

4.8 Centralised Monitoring

Trials may be monitored using centralised monitoring on the basis of a risk assessment. Centralised monitoring can be used in addition to on-site visits.

For low-intervention trials centralised monitoring may be performed instead of routine on-site monitoring visits.

Centralised monitoring will be performed by remote evaluation of accumulating data as defined in the monitoring plan. In addition, details of data evaluation carried out by data managers or statisticians may be included in the data management plan.

The trial data manager or statistician or other suitably qualified person will:

- Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations
- Examine data trends such as the range, consistency, and variability of data within and across sites
- Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems
- Analyse site characteristics and performance metrics

If there are sites which are not producing data consistent with majority of other sites or are not performing in the same way as the majority of sites, these sites and/or processes will be selected for on-site monitoring, until they are functioning as expected.

Centralised monitoring activities and observations will also be reported using the monitoring report template. If a different report template will be used this will be described in either the monitoring plan or the data management plan.

5 DOCUMENTATION

Monitors, in addition to reports, can write a Note To File to document deviations from the protocol or to clarify other ambiguities. The coordinating investigator should always be informed in writing of discrepancies detected during monitoring.

The following should be filed in the sponsor's Trial Master File:

- The Monitoring Plan
- All signed monitoring reports
- Notes to File
- Copies of significant communication with site staff (e.g. answers to questions about protocol procedures, trial updates, new letters etc.)
- Other documentation generated during monitoring activities

The copies of the initiation, routine and close out visit reports and the monitoring log must be filed in the Investigator's Site File.

6 NON-COMPLIANCE MANAGEMENT

All non-compliance should be handled according to the procedures for handling non-compliance of the individual health trust / institution and to SOP Protocol Deviation Handling.

7 REFERENCES

7.1 External References

- Legemiddelloven
- Forskrift om legemidler (legemiddelforskriften)
- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) Section 5.18.
- REGULATION (EU) No 536/2014 of The European Parliament and of the Council on clinical trials on medicinal products for human use

7.2 Internal References

- SOP Protocol Deviation Handling
- SOP Quality and Risk Management

8 ATTACHMENTS

- Trial Initiation Report
- Monitoring Report
- Close-out Monitoring Report
- Biobank Monitoring Report
- Query list
- Trial Handover Procedure and Checklist
- Green Light for Start of Trial Recruitment
- Data Processing Agreement for Monitoring Services
- Data Verification Plan template

9 DEFINITIONS

SOP Definitions.

Abbreviation	Term
eCRF	electronic Case Record Form
CV	Curriculum Vitae
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
SOP	Standard Operating Procedure
TMF	Trial Master File

10 CHANGES SINCE LAST VERSION

CT SOP version no 1.0

Main changes from LM SOP 2.14: Added use of Green Light Document for start of trial recruitment. Added specifications required about source data verifications. Specified and detailed responsibilities of the monitor and the lead monitor role, including Protocol Deviation Handling Plan and Data Processing Agreement. Rectified minor mistakes. Removed report templates in Norwegian. Adapted to the wording of the clinical trial regulation no 536/2014