1 PURPOSE

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe how clinical trials should be monitored.

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

The aim of monitoring is to verify that:

- The rights, well-being and integrity of the trial participant are protected.
- 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.

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

3 RESPONSIBILITIES

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

Tasks can be delegated. Delegation should be documented in writing.

4 APPROACH AND RESPONSIBILITIES

4.1 SPONSOR'S RESPONSIBILITIES AND DUTIES

Sponsor is responsible for appointing a monitor and having a monitoring agreement of the trial in place. Clinical Trials Units at the university hospitals will be able to provide monitoring or inform about other hospitals that do.

Sponsor is also responsible for having a monitoring plan in place. This should be archived in the Trial Master File (TMF).

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 have a relationship to the sponsor representative or to site staff.

Sponsor 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 TMF.

Sponsor should define the level and degree of monitoring. Usually, the monitoring will 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 logged and handled in the study.

The tasks described above can be delegated to the Principal Investigator in a single center trial or the National Coordinating Investigator in a multi-center trial.

The monitor will send a report from each monitoring visit to the sponsor within 14 calendar days. Sponsor, or sponsor's designee, should review and sign the monitoring reports within 14 calendar days and return a signed copy to the monitor.

4.2 PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES AND DUTIES

The Principal Investigator is responsible for being available and ensuring facilities required for monitoring is in place. Facilities include an office place, access to study documents, source data and other relevant documentation and equipment to be monitored.

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 get their own log-in credentials to the medical records (read access, only) 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 SDV or print out all relevant medical notes for all patients to be SDV'ed.

The Principal Investigator is responsible for making corrections and following up on deviations and actions identified in the monitoring report. 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.

Handling of deviations is described in SOP Note to File.

4.3 MONITOR'S RESPONSIBILITIES AND DUTIES

Monitor should have knowledge about the Investigational Medicinal Product (IMP), the study protocol, patient information and consent form, ICH-GCP and applicable laws and regulations.

Monitor should follow the monitoring plan and relevant study procedures defined by sponsor and Principal Investigator.

After each monitoring, both on site and off site, the monitor should complete a report. The report should be completed and forwarded to the sponsor as a pdf-document attached to an e-mail within 14 calendar days. Attachment 1 with the action list to be handled by the site should be attached. At the same time, the action list should be sent to the site, as a pdf-document attached to an e-mail. The whole report can be sent to the site, as well, but this is not mandatory, except from the Initiation Visit Report, which should be filed in the ISF.

4.4 INITIATION VISIT

An initiation visit should be performed at each study site before the study is initiated to ensure all required documents and IMPs are in place. For small studies the initiation visit can be combined with the start-up meeting, see SOP Søknadsprosess, godkjenninger og oppstart and Mal agenda oppstartsmøte.

Monitor will make an appointment with the Principal Investigator or designee. If applicable and described in the monitoring plan, an appointment will also be made with the pharmacy, laboratory or other units to be involved in the trial.

After the initiation visit, the monitor should complete the Initiation Visit Report, which can be found in Norwegian here and English here.

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 has to confirm this is resolved before the eCRF is made available to the site and enrolment can start.

4.5 INITIATION VISIT REPORT

In general, any cross in grey boxes in the initiation visit report template should be commented upon. In the comment field, please refer to the question number to which the comment belongs.

To section 2, the date and version no of the current protocol and informed consent form, should be entered in the table. The table should be modified if more than one version of the documents are in use at the same time.

To section 5, all study staff listed on the delegation log, should file a signed and dated copy of their CV in the ISF. The Principal Investigator must document ICH-GCP knowledge either on their CV or by a training certificate. This is also recommended for other study staff performing study specific tasks as obtaining informed consents, collecting data or evaluating the study participant. All study staff performing study specific tasks should also document that they have received protocol and procedure specific training either by a training certificate or on a study specific training log.

To section 9, specify whether an IB or a SmPC is used in this study and specify the version and/or date of the current document. IBs are usually used for IMPs without marketing approval, while SmPCs are used for IMPs with marketing approval. IBs should be revised annually. If there is no new information available, the producer should provide a document confirming this. The latest version of the SmPC can be found at https://www.legemiddelsok.no/.

To section 10, attention should be paid to study specific equipment and/or equipment important to the end points in the study. In these cases, ensure there are routines in place for service, validation and/or calibration. Further, all lab reference values (original, as well as updated values), should be available as part of the study documentation at the site. In addition, there should also be documentation in place showing the lab is accredited or ISO-certified. Ensure the accreditation or ISO-certification still is valid.

If a check of the local biobank is part of the monitoring plan, refer to the report template for monitoring biobanks in Norwegian here and English here.

To section 13, in case there is an electronic Case Report Form (eCRF) to be used at this site, the monitor should inform the data manager for the study when the CRF can be made available for the site staff, i.e. when there are no major issues pending. In a multi-center trial, this will apply only to sites where all major issues are closed.

To section 14, the monitor should set a due date which reflects the seriousness of the deviation when completing the actions to be taken by the site staff. In case of serious deviation requiring urgent action, a solution could be expected within a week or two. For deviations without any urgency, a solution could be expected within a month or two.

4.6 MONITORING VISIT

The Monitoring Plan should be archived in sponsor's TMF.

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

The Monitoring Plan should also clearly define what to monitor at the monitoring visits.

In case the Monitoring Plan requires monitoring of a biobank, the monitor should complete a specific report for the checks performed in Norwegian here and English here. The Monitor is responsible for informing the Principal Investigator about missing documents, deviations found between source data and CRF, or any actions required to ensure the trial is ran according to the study protocol, laws and regulations and ICH-GCP. All actions and corrections required should be performed and documented accordingly by the site personnel. The monitor is not allowed to amend source documents or enter data into the CRF.

After each monitoring visit the monitor should complete the Monitoring Visit Report, which can be found in Norwegian here and English here.

The Principal Investigator in a single centre trial or the National Coordinating Investigator in a multi-centre trial can amend the monitoring plan based on e.g.:

- 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 preclinical studies

4.7 MONITORING VISIT REPORT

In general, any cross in grey boxes in the monitoring visit report template should be commented upon. In the comment field, please refer to the question number to which the comment belongs.

To section 2, the date and version no of the current protocol and informed consent form, should be entered in the table. The table should be modified if more than one version of the documents is in use at the same time.

To section 4, note which version(s) of the informed consent form(s) that has been used at the site and for which subjects the informed consent form and process where checked. In the subject's medical notes it should be stated that the subject has been given oral and written information, had the chance to ask questions, given time to consider participation and given a copy of the signed informed consent form. Checking informed consent forms includes a check of the following:

- Is the informed consent form signed before any study specific procedures have been undertaken?
- Is the correct version of the informed consent form used? Is there a version no and version date in the header or footer? Is the version approved by REK?
- Are all fields to be completed filled in?
- Is the contact information (name, address and phone no) correct?
- Have the subjects (or subject's representative) signed and dated themselves? Is the date complete with day, month and year? If the signature is not legible, it is recommended that the name is written in typed letters, as well.
- Is the person informing the subject given this task on the delegation log? Is the date complete with day, month and year? If the signature is not legible, it is recommended that the name is written in typed letters, as well.

To section 5, document for which subjects inclusion and exclusion criteria have been checked. Also document for which subjects and for which visits source data verification has been performed. 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. The list should be attached to the report when sent to the site and the monitor should keep a copy, to be able to verify all deviations are corrected accordingly.

To section 6, document for which subjects and for which visits AEs and SAEs have been checked. In case of deviations, please comment. Further, check that the annual report is sent to NoMA 1 year + up to 60 days after the approval first was given. The annual report should include SUSARs and SSARs only; SAEs are included in the study report.

To section 7, for studies with marketed products, drug accountability logs should be available for each subject. For studies with IMP produced specifically for the study, there should additionally be drug accountability logs at site level. Templates can be found at NorCRIN. In case other templates or records are used, these should contain all required information, e.g. dose dispensed, batch number and expiry date.

To section 8, all lab reference values (original, as well as updated values), should be available as part of the study documentation at the site.

If a check of the local biobank is part of the monitoring plan, refer to the report template for monitoring biobanks in Norwegian here and English here.

To section 13, the monitor should set a due date which reflects the seriousness of the deviation when completing the actions to be taken by the site staff. In case of serious deviation requiring urgent action, a solution could be expected within a week or two. For deviations without any urgency, a solution could be expected within a month or two. For some deviations, a solution cannot be expected until the subject returns for the next visit. In these cases, the expected date for the next visit should be used as due date.

4.8 CLOSE-OUT VISIT

A close-out visit should be performed at each site after the last patient 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.

After the close-out visit the monitor should complete the Close-out Visit Report, which can be found in Norwegian here and English here.

4.9 CLOSE-OUT VISIT REPORT

In general, any cross in grey boxes in the close-out visit report template should be commented upon. In the comment field, please refer to the question number to which the comment belongs.

To section 11, the monitor should set a due date which reflects the seriousness of the deviation when completing the actions to be taken by the site staff. In case of serious deviation requiring urgent action, a solution could be expected within a week or two. For deviations without any urgency, a solution could be expected within a month or two.

4.10 MONITORING OF BIOBANK

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

After a biobank monitoring visit the monitor should complete the Biobank Monitoring Visit Report, which can be found in Norwegian here (link) and English here (link).

4.11 BIOBANK MONITORING VISIT REPORT

In general, cross in any grey boxes in the monitoring of biobank report template should be commented upon. In the comment field, refer to the question number to which the comment belongs.

To section 1.1 and 1.2, there should be contact information available to the principal investigator and other relevant site personnel to be contacted in case the samples have to be relocated, for instance.

To section 1.3, use the comment field to describe whether a central surveillance system is used (electronically temperature surveillance) or if it is done manually. Manually surveillance is recommended daily.

To section 1.4, use the comment field to describe what happens if the temperature exceeds recommended limits.

To section 1.5, the department/clinic ought to have an emergency freezer. The personnel should know where it is placed.

To section 1.7, check with the Technical Department that set up the storage facility.

To section 3.1, the samples should not be marked with directly identifiable personal information.

To section 3.4, if no, use the comment field to describe how the site keeps an overview of the biobank. In addition describe whether there is an overview over samples that have been taken out and refreezed again.

To section 3.6, the responsible person has the responsibility for the samples to be packed and shipped according to local regulations, see e.g. shipment of biological material published by “Direktoratet for samfunnssikkerhet og beredskap”.

To section 3.7, when samples are going to be shipped from one site to another, there must be an agreement in place. If both sites are taking part in the study, the shipment of samples could be described in a collaboration agreement. If the samples are going to be shipped to a third party, there should be a Material Transfer Agreement (MTA) in place. Remember, the person responsible for shipment must ensure that the trial subject has consented to this, and the samples generally need to be de-identified.

To section 6, the monitor should set a due date which reflects the seriousness of the deviation when completing the actions to be taken by the site staff. In case of serious deviation requiring urgent action, a solution could be expected within a week or two. For deviations without any urgency, a solution could be expected within a month or two.

4.12 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.

4.13 MONITOR HANDOVER CHECKLIST

In case the monitoring of a site has to be handed over to another monitor, the previous 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, as well as together with monitors’ CVs in the TMF, to document monitor’s qualifications.

4.14 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.

4.15 DOCUMENTATION

All monitoring reports should be filed in the Trial Master File (TMF).

5 HANDLING OF DEVIATIONS

Documentation of non-compliance in the individual study should be handled according to SOP Note to File and according to the procedures for handling non-compliance of the individual health facility / institution.
How to close a deviation and possible escalation should be in accordance with SOP Avvikshåndtering.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Helseforskningsloven
- Legemiddelloven
- Forskrift om klinisk utprøving av legemidler til mennesker 2009-10-30-1321 (KLUT-forskrift)
- Forskrift om legemidler (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 Note to File
- SOP Avvikshåndtering
- SOP Quality and Risk Management

7 ATTACHMENTS

- 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 Monitoring research biobank report
- Template Query list
- Template Handover checklist

8 DEFINITIONS

- Definisjoner

9 CHANGES FROM PREVIOUS VERSION

Version 3.1 replaces version 3.0. Translated to English. Specified timeline for sending and reviewing the monitoring reports. Added spesification about how to provide the monitor with access to the medical records. Focus on sponsor's responsibility for having a system for collection of deviations and for other functions to follow to procedure. Removing the need for the Principal Investigot to sign the reports. Added sections on how the reports should be filled in. Reference to the monitoring logg is removed.