1 PURPOSE

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

The SOP should ensure that national and international laws and regulations and ICH Guideline for Good Clinical Practice (ICH-GCP) specified in the SOP Legislation and Guidelines 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

This SOP is valid for all clinical drug trials sponsored by hospitals that have implemented the NorCRIN SOPs and for trials for which this SOP has been accepted by sponsor.

3 RESPONSIBILITIES

The monitor is responsible for monitoring according to the monitoring plan. The monitor should also inform the coordinating investigator if there is a change in risks due to either poorer or better quality that could warrant a change in the monitoring plan.

4 APPROACH

4.1 Monitor's qualifications and tasks

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

The monitor should

- Facilitate a risk evaluation with the trial team, if requested
- Assist the trial team to develop a monitoring plan based on the risk evaluation, if requested
- Develop a cost estimate for the monitoring activities in the trial
- Assist the trial team to develop a Protocol Deviation Handling Plan, if requested

The monitoring plan should be specific upon which data variables to be source data verified by the monitor. This can be done by describing the modules to be verified directly in the monitoring plan or by adding a data verification plan as an attachment to the monitoring plan. It is recommended that the monitor works closely with the data manager in trials were the eCRF is produced locally, to ensure the monitoring plan and the data validation plan is complementary.

The monitor should also consider and discuss with the data manager, statistician and/or trial group, whether interim analysis or data monitoring committee meetings during the trial require additional monitoring activities, and if so, include this in the monitoring plan.

In case the monitor is not employed at sponsor institution, a Data Processing Agreement must be signed. It can be included in the monitoring agreement or as a separate document. Monitor should assist sponsor to get this agreement in place.

Monitor should follow the Monitoring Plan and relevant trial procedures defined by coordinating investigator.

After each monitoring visit, both on-site and off-site, the monitor should complete a report. The report should be completed and forwarded to the coordinating investigator as a pdf-document including attachment 1, the action list, within 14 calendar days., The action list should be sent to the site in parallel, as a pdf-document attached to an e-mail. The complete report can be sent to the site, as well, but this is not mandatory. However, for the initiation visit report, it is a requirement to file a copy of the complete report in the site's ISF.

Issues considered protocol deviations should be reported according to protocol specific procedure.

4.2 Lead monitor's tasks

In national and international studies with several monitors involved, the monitor at the coordinating investigator's institution will become the lead monitor for the trial. The lead monitor will be the liaison between the coordinating investigator and the monitors.

In addition to the tasks listed above, the lead monitor should

- Share the risk assessment, monitoring plan, cooperation agreement and cost estimate, as applicable, with the other monitors, including accounting information required for invoicing
- Assist the sponsor/coordinating investigator with having a Data Processing Agreement in place with monitors employed at other institutions than the sponsor institution
- Provide training in the monitoring plan
- Present the monitoring plan at common initiation meetings, if requested
- Answer questions from monitors and others related to the monitoring in the trial
- Schedule phone meetings and other meetings upon request or when required
- Share information from the coordinating investigator and trial team, as applicable, on an ongoing basis

4.3 Initiation visit

An initiation visit should be performed at each trial site before the trial 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 Application Process, Approvals and Start-up and mal Start-up Meeting Agenda.

Monitor will make visit arrangements with the principal investigator (PI) 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 Trial Initiation Report

The monitor will decide whether the site is ready to start enrolment or not, based on the issues identified. Examples of major issues are; pending approvals or agreements, missing/incomplete delegation log, insurance certificate, source data list, trial drug or training of trial personnel. When all major outstanding issues are resolved and the monitor considers the site is ready to start enrolment, the monitor inform the principal investigator and project leader. If applicable, access to the eCRF system will be given to the site staff upon forwarding a completed and signed Green Light for Start of Trial Recruitment to the data manager, with copy to the principal investigator and coordinating investigator.

4.4 Initiation visit report

Any cross in grey boxes in the initiation visit report template should be commented. In the comment field, please refer to the relevant question number when adding the comment.

The “not applicable” box should be used if the topic is not relevant for the trial (e.g. blinding in an open trial) or not required to be checked according to the monitoring plan (e.g. biobank is used, but the monitoring plan does not require the monitor to check the facilities).

The “not checked” box should be used if the topic is relevant for the trial and/or part of the monitoring plan, but when the monitor for whatever reason did not perform the check during the actual visit. The reason for why the check was not performed, must be explained in the comment field (e.g. due to time constraints the Investigator Site File was not checked at this visit).

In section 1, enter the date and version no. of the current protocol and informed consent form. The table should be modified if more than one version of the documents are in use at the same time.

In section 4, all trial staff members listed on the delegation log, should file a current copy of their CV in the Investigator Site File (ISF). The PI must document ICH-GCP knowledge, either on their CV or by a training certificate. This is also recommended for other trial staff members performing trial specific tasks as obtaining informed consents, collecting data or evaluating the trial participant. All trial staff performing trial specific tasks should also document that they have received protocol and procedure specific training either by a training certificate or on a trial specific training log.

In section 8, specify whether an Investigator’s Brochure (IB) or a Summary of Product Characteristics (SmPC) is used as referral document in this trial and specify 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 manufacturer should provide a document confirming this. The latest version of the SmPC can be found at https://www.legemiddelsok.no/.

In section 9, attention should be paid to trial specific equipment and/or equipment important to the endpoints in the trial. 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 trial 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 Biobank Monitoring Report

In section 12, if relevant, the monitor should inform the data manager for the trial when the eCRF can be made available for the site staff, i.e. when there are no major issues pending.

For pending issues, 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 should be expected within a week or two. For deviations without any urgency, a solution could be expected within a month or two.

4.5 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.

In case the Monitoring Plan requires monitoring of a biobank, see section 4.10.

The Monitor is responsible for informing the PI about any missing documents, deviations found between source data and CRF, or any actions required to ensure the trial is run according to the trial 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.

4.6 Monitoring visit report

After each monitoring visit the monitor should complete the Monitoring Report any cross in grey boxes in the monitoring visit report template should be commented. In the comment field, please refer to the relevant question number when adding a comment.

In section 2, enter the date and version number of the current protocol and informed consent form. The table should be modified if more than one version of the documents is in use at the same time.

In 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 the consent process where checked. In the subject's medical notes it should be stated that the subject has received oral and written information, had the opportunity to ask questions, had time to consider participation and was given a copy of the signed informed consent form. Checking informed consent forms includes the following:

- Is the informed consent form signed before any trial specific procedures have been done?
- Is the correct version of the informed consent form used? Is version number and date present in the header or footer? Is the version approved by the Regional Committees for Medical and Health Research Ethics (REK)?
- Are all applicable fields completed?
- 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 (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 delegated 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.

In section 5, record for which subjects inclusion and exclusion criteria have been checked. Also record for which subjects and for which visits source data verification has been performed. If queries cannot be entered directly into an eCRF, they should be listed in the report or on a Query List. The list should be attached to the action list when sent to the site and the monitor should keep a copy, to be able to verify that all queries are resolved.

In section 6, record for which subjects and visits AEs and SAEs have been checked. In case of deviations, please comment. Further, check that the annual safety report, Drug Safety Update Report (DSUR), is submitted in CTIS in time (yearly from date of birth + up to 60 days for submission) after the birth date.

In section 7, for studies with marketed products, drug accountability logs should be available for each subject. For studies with trial specific produced IMP, 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 to whom, when and by whom, batch number and expiry date.

In trials with blinded and unblinded monitor, the blinded monitor should complete a monitoring report, except for section 7 regarding investigational medicinal products. The unblinded monitor completes a separate report, but section 7 only. The blinded monitor forward the report to coordinating investigator (action list to investigator), the unblinded monitor should forward the report/action list to unblinded trial staff only and ensure the unblinded trial staff follow up on action items. The unblinded trial staff should store the report with limited access to blinded trial staff during the trial, and the unblinded monitor should keep unblinded reports electronically at a secure place with limited access to the blinded monitor. When the database is locked the unblinded reports can be filed in the site's ISF and copies should be forwarded to coordinating investigator for filing in TMF. Issues considered protocol deviations should be reported according to protocol specific procedure keeping the blinding whenever possible. In some studies, the coordinating investigator may be unblinded.

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

If a check of the local biobank is part of the monitoring plan, refer to Biobank Monitoring Report.

In section 12, monitoring should be risk-based. It is therefore important that the monitor informs the coordinating investigator whenever the monitor uncovers deviations that warrant a change in the monitoring plan for the entire trial or for that specific site. This information should be highlighted in the email and the monitor should ensure that an evaluation is given by coordinating investigator.

For pending issues, 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 should be expected within a week or two. For deviations without any urgency, a solution should 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.

4.7 Close-out visit

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

After the close-out visit the monitor should complete the Close-out Monitoring Report .

4.8 Close-out visit report

Any cross in grey boxes in the close-out visit report template should be commented. In the comment field, please refer to the relevant question number for the comment.

To section 4, in trials with blinded and unblinded monitor, the blinded monitor should complete a close-out visit report, except section 4 regarding investigational medicinal products. The unblinded monitor completes a separate report, but section 4 only. The blinded monitor forward the report to coordinating investigator (action list to investigator), the unblinded monitor should forward the report to unblinded trial staff only. The unblinded trial staff should store the report with limited access to blinded trial staff during the trial, and the unblinded monitor should keep unblinded reports electronically at a secure place with limited access to the blinded monitor. When the database is locked the unblinded reports can be filed in the site's ISF and copies should be forwarded to coordinating investigator for filing in TMF. In some studies, the coordinating investigator may be unblinded.

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

It is recommended that the monitor lists coordinating investigator's tasks for follow-up as pending issues, as a help and reminder for the coordinating investigator. This applies only to the close-out visit report at coordinating investigator's site. Proposed text is as follows:

8.1 Please report the trial as completed according to the hospital's internal guidelines.

8.2 Please report the trial as completed in CTIS within 15 days after the trial is completed in each participating country, in all countries in the EEA and in the last country worldwide.

8.3 Please send a final report for the trial in CTIS within 12 months after the trial is completed.

8.4 Please update CTIS with the results of the trial within 12 months after the trial is completed.

8.5 Please update trial information on the hospital's web pages as soon as possible after the trial is completed.

8.6 Please update trial information on ClinicalTrials.gov within 30 days after the trial is completed, if the trial is registered there.

4.9 Off-site monitoring

Off-site monitoring is defined as monitoring of a site by phone or videoconference. 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.

To perform an efficient off-site monitoring visit, the site staff should be prepared. It is therefore recommended to e-mail the investigator and trial coordinator in advance with information about the purpose of the visit and items to be discussed. The e-mail should also list documents to be checked, so the site staff can ensure they are easily available during the off-site monitoring. Documents to be checked may include patient records, informed consent forms, as well as documents from the ISF. The participation of the investigator is recommended, at least at a part of the off-site monitoring, to ensure investigator's oversight of the trial.

To perform an efficient off-site monitoring visit, also the monitor should be well prepared, including selecting the patients to be source data verified before the off-site monitoring visit.

4.10 Off-site monitoring visit report

NorCRIN's visit report templates should be used as is, with a cross for "not checked" for those questions not being checked during the off-site monitoring. No fields or sections should be removed from the template.

Any cross in any grey boxes in the monitoring report template should be commented. Provide "off-site monitoring" as reason if there are questions that cannot be answered because the monitoring is being done by phone or videoconference.

4.11 Biobank monitoring

Sometimes the risk assessment indicates that the monitor should monitor also a study's biobank. In case samples are stored in freezers not part of a hospital's regular sample repository, a verification by the monitor to ensure the samples are registered, temperature monitored and stored properly, may be warranted.

4.12 Biobank monitoring report

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

In section 1.1 and 1.2, record contact information available for the PI and other relevant site personnel to be contacted in case the samples have to be relocated, for instance.

In section 1.4, 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.

In section 1.5, use the comment field to describe what happens if the temperature is outside recommended limits.

In section 1.6, the department/clinic ought to have emergency equipment. The personnel should know where it is placed.

In section 1.8, check with the Technical Department responsible for the set up of the storage facility.

In section 3.3, the samples should not be marked with directly identifiable personal information.

In section 3.4, the samples should have labels adapted to the type of freezer and the duration of the storage. It must be possible to read the print and the labels should stick to container for the duration of the storage.

In section 3.7, 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.

In section 3.9, the responsible person should ensure the samples are packed and shipped according to local regulations, see e.g. shipment of biological material published by "Direktoratet for samfunnssikkerhet og beredskap".

In section 3.10, when samples are going to be shipped from one site to another, there must be an agreement in place. If both sites are participating in the trial, 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.

For pending issues, 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 should be expected within a week or two. For deviations without any urgency, a solution should be expected within a month or two.

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 about the monitoring status of the site by completing Trial Handover Procedure and 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.

5 HANDLING OF DEVIATIONS

Documentation of non-compliance in the individual trial 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

- REGULATION (EU) No 536/2014
- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) chap. 5.18
- Beste praksis for norske biobanker (27.05.2019)

6.2 Internal references

- SOP Protocol Deviation Handling
- SOP Quality and Risk Management
- SOP Monitoring
- Protocol Deviation Handling Plan
- Trial Initiation Report
- Monitoring Report
- Close-out Monitoring Report
- Biobank Monitoring Report
- Trial Handover Procedure and Checklist

- Query List
- Green Light for Start of Trial Recruitment
- Data Verification Plan template

7 ATTACHMENTS

None

8 DEFINITIONS

Definitions

9 CHANGES SINCE LAST VERSION

CT SOP version no 1.0

Main changes from LM SOP monitoring from monitors, version 3.3. Added use of Green Light for Start of Trial Recruitment Document. Added use of DSURs in international trials. Added specifications required about source data verifications. Specified and detailed responsibilities of the monitor and the lead montior role, including Protocol Deviation Handling Plan and Data Processing Agreement. Rectified minor mistakes. Removed Norwegian monitoring report templates. Adapted to the wording of the clinical trial regulation no 536/2014 includingtimelines for reporting end of trial. Updated best practice document for biobanks.