1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the process for detecting, documenting, assessing, tracking, and closing of protocol deviations (PDs) detected by study personnel at site or by sponsor, e.g. during monitoring (including data monitoring by data managers) of clinical trials.

This SOP ensures that issues are managed in compliance with ICH Guideline for Good Clinical Practice (ICH-GCP) and national and international laws and regulations, specified in the SOP Referansedokument.

2 SCOPE

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

3 RESPONSIBILITIES

The sponsor has the overall responsibility for handling PDs.

The sponsor or designee(s) is responsible for addressing protocol deviations, developing and implementing appropriate CAPAs (corrective action, preventative action) as well as defining the impact of deviations.

Principal Investigators (PIs) and study site team (e.g., study nurse/coordinators as well as sponsor functions such as study statistician, monitors, data managers) are all responsible for detecting protocol deviations and notifying the sponsor and authorities as applicable and implementing CAPAs. The sponsor is responsible for assisting the site with detection and handling deviations.

The sponsor's responsibilities shall be described in the governing documents (quality system) of the individual health trust / the individual institution. Tasks can be delegated to qualified staff. The delegation of tasks shall be documented, for example, in written agreements.

4 PROCEDURES

4.1 Definitions

Protocol Deviation (PD): Any change, divergence or departure from the study design or procedures defined in the protocol.

Important Protocol Deviation (IPD): A PD that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, enrolling patients that do not meet key eligibility criteria; incorrect administration of study drug; absence of source documents; failure in recording or incorrectly recording the primary efficacy variable(s)

Not Important Deviation (NID): A PD that is unlikely to have a significant effect on the rights, safety, or well-being of subjects and/or the quality or integrity of data. For example, isolated occurrence of out-of-window visit for a non-pivotal measurement.

Protocol Deviation Handling Plan (PDHP): A Plan describing the approach for detecting, documenting, assessing, tracking, and closing PDs. This plan can be utilized as a stand-alone plan or can be incorporated into an existing plan such as the protocol.

4.2 Before Study Start

To ensure a high degree of adherence and compliance to the study protocol, the protocol should be designed with input from the Principal Investigator in single center studies/National Coordinating Investigator in multicentre studies (PI/NCI), statistician, Principal Investigators (PI), monitors, and study site personnel. It is highly recommended to seek patient and public involvement (brukermedvirkning). A Protocol Deviation Handling Plan (PDHP) should be developed by the PI/NCI for each study prior to first patient enrolled.

A system for reporting and tracking of PDs should be established. Use of real-time data recording on web-based electronic systems is highly preferable as it enables rapid identification of protocol deviations. If an electronic system for reporting of protocol deviations is not available, a Protocol Deviation Notification and Tracking Form may be provided to the site to document deviations.

The study team, including the investigator, site personnel and sponsor functions should be trained in their obligations in the PDHP.

4.3 During the Study: Detecting, Documenting, and Reporting Protocol Deviations

Protocol deviations may be detected by the PI, study coordinator/study nurse, monitor, data manager, statistician or other function.

It is important to define the protocol deviations requiring ongoing reporting in the PDHP. At least the following should be included:

1. Subjects entered into the study not meeting the entry criteria.
2. Subjects who developed withdrawal criteria (from treatment or study) during the study but were not withdrawn.
3. Subjects who received the wrong study treatment or incorrect dose.
4. Subjects who received an excluded concomitant treatment.
5. Failing to collect data necessary to interpret the primary endpoint, and main secondary endpoints as applicable. This should be consistent with the data defining the per protocol analysis if any.
6. Other serious breaches according to Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol
7. Risks identified in the risk evaluation as not acceptable have occurred and are important

Other protocol deviations that can be extracted from the study database and that do not fall into any of the categories above can be listed if relevant.

Protocol deviations detected by the site should be reported to the PI/NCI using the Protocol Deviation Notification and Tracking Form by means described in the PDHP in a timely manner.

Protocol deviations detected by the sponsor will be reviewed and acknowledged by the PI as applicable. Deviations detected by Data Management or Biostatistics may be communicated if needed to the PI for review and acknowledgement using the data query process.

For countries where reporting of serious breaches are mandatory according to local legislation, the PI/NCI and/or the site must adhere to specific timelines for mandatory reporting required by regulatory bodies. An example of a deviation that is of significance for patients in the European Economic Area (EEA) is a late or erroneous reporting of new safety data. Important deviations may need to be reported within 7 calendar days to health authorities in the EEA when a deviation has or could have represented a risk to the patient or is a violation of his/her rights.Reporting is mandatory if the deviation has occurred in a clinical trial center in the EEA or when the

deviation has occurred outside the EEA but the deviation or knowledge about the deviation could be of significance for patients in the EEA.

The monitor ensures the site maintains documentation of protocol deviations and associated CAPAs as applicable.

4.4 Sponsor Evaluation and Tracking of Protocol Deviations

Upon receipt of the Protocol deviation notification and tracking form or notification of entry into the EDC from the study site, the PI/NCI acknowledges receipt and handles the deviation in accordance with the PDHP.

Upon receipt of a "Protocol Deviation Notification and Tracking Form", the PI/NCI will need to enter the information into a log for the trial, either Protocol Deviation Log Single Center Study or Protocol Deviation Log Multicenter Study.

The PI/NCI ensures development of study specific listing and/or summary for tracking and review of protocol deviations across all study sites to ensure protocol deviations are appropriately classified, monitored and resolved to closure.

The protocol deviation listing/summary will be reviewed by appropriate study team members at the frequency defined in the PDHP.

The action taken by the site in response to a protocol deviation is to be captured on the notification form.

The PI/NCI classifies the deviation as Important or Not Important, for reporting purposes.

4.5 Follow-up of Protocol Deviations

Periodic reviews by the study team will include verification of appropriate actions (CAPAs).

The PI/NCI reviews the corrective and preventative actions on previous protocol deviation and ensures proper and timely resolution.

When appropriate, the PI/NCI provides additional training and support to the site to assure a previously reported protocol deviation does not reoccur. Training should be documented appropriately.

The PI/NCI will educate all sites about observed protocol deviations as described in the PDHP and ensure CAPAs if any have been implemented.

4.6 Noncompliance Escalation

If deviations at site are not closed within agreed timelines (or a plan for closure is not communicated to the monitor within the appropriate deadline) the lack of deviations follow up should be escalated to the PI/NCI. If the deviations related to PI/NCI's sponsor tasks or to PI/NCIs own site are not closed within agreed timelines or reasonable time, the deviations should be escalated to the sponsor representative. It is recommended that the reporter's manager pursues the escalation.

In case of disagreement about a deviation's seriousness, the PI/NCI could explain why he/she considers this not to be a deviation. This should be documented and archived in the Trial Master File (TMF). If the explanation from the PI/NCI is unacceptable and the deviation is critical, unambiguous or unlawful, the sponsor representative should be asked for a second opinion. As a last resort, the person who has detected the deviation can independently report the deviation to the Norwegian Medicines Agency / Regional Committees for Medical and Health Ethics or other relevant Competent Authority.

4.7 Records

The protocol deviation summary/listing will be filed in the TMF and the site will archive the summary/listing concerning their site in the Investigators Site File (ISF).

5 NON-COMPLIANCE MANAGEMENT

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

6 REFERENCES

6.1 External references

Mehra M, Kurpanek K, Petrizzo M, et al. The life cycle and management of protocol deviations. Therapeutic Innovation and Regulatory Science 2014;48(6):762-777.

ICH Guideline for Good Clinical Practice (GCP) E6 (R2) ICH GCP

ICH Guideline: Structure and content of clinical study report Topic E3

ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers

Guideline for the notification of serious breaches of Regulation (EU) No 536/2014

6.2 Internal references

None

7 ATTACHMENTS

- Protocol Deviation Handling Plan (PDHP)
- Protocol Deviation Notification and Tracking Form
- Protocol Deviation Log Single Center Study
- Protocol Deviation Log Multicenter Study

8 DEFINITIONS

- Definisjoner

9 CHANGES SINCE LAST REVISION

New SOP version 1.0. It replaces SOP 1.06 Note to File and SOP 1.08 Avvikshåndtering.