PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the process for detecting, documenting, assessing, tracking, and closing 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 compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP legislation and guidelines.

1 SCOPE

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

2 RESPONSIBILITIES

The sponsor has the overall responsibility for handling PDs.

The 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.

The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf. Transfer of duties shall be specified in a written agreement.

The Coordinating Investigator (CI) should address protocol deviations, develop and implement appropriate CAPAs (corrective action, preventative action) as well as define the impact of deviations.

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

3 PROCEDURES

3.1 Definitions

Protocol Deviation (PD): Any change, divergence or departure from the trial 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 trial 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 trial 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.

3.2 Before Trial Start

To ensure a high degree of adherence and compliance to the trial protocol, the protocol should be designed with input from the CI, statistician, PI, monitors, and trial site personnel. It is highly recommended to seek patient and public involvement (brukermedvirkning). A Protocol Deviation Handling Plan should be developed by the CI for each trial 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.

3.3 During the Trial: 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 trial not meeting the entry criteria.
2. Subjects who developed withdrawal criteria (from treatment or trial) during the trial but were not withdrawn.
3. Subjects who received the wrong trial treatment or incorrect dose.
4. Subjects who received a prohibited 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 EMA 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

In addition NIDs that are helpful to understand the conduct of the trial can be reported.

Other protocol deviations that can be extracted from the trial 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 CI by means described in the PDHP in a timely manner.

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

The CI must adhere to specific timelines for mandatory reporting of serious breaches 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 must be reported within 7 calendar days to competent 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.

3.4 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 trial site, the CI acknowledges receipt and handles the deviation in accordance with the PDHP.

Upon receipt of a “Protocol Deviation Notification and Tracking Form”, the CI 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 CI ensures development of trial specific listing and/or summary for tracking and review of protocol deviations across all trial sites to ensure protocol deviations are appropriately classified, monitored and resolved to closure.

The protocol deviation listing/summary will be reviewed by appropriate trial 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 CI classifies the deviation as Important or Not Important, for reporting purposes.

3.5 Follow-up of Protocol Deviations

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

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

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

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

3.6 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) this must be escalated to the CI. If the deviations related to CI's sponsor tasks or to CI's own site are not closed within agreed timelines or reasonable time, this 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 CI 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 CI 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 Competent Authority.

3.7 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).

4 NON-COMPLIANCE MANAGEMENT

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution.

5 REFERENCES

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

- ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers
- EMA Guideline for the notification of serious breaches of Regulation (EU) No 536/2014
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use

5.2 Internal references

None

6 ATTACHMENTS

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

7 DEFINITIONS

- SOP Definitions

Abbreviation	Term
CAPA	Corrective Action, Preventative Action
CI	Coordinating Investigator
CRO	Contract Research Organisation
EDC	Electronic Data Capture
EEA	European Economic Area
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IPD	Important Protocol Deviation
ISF	Investigator's Site File
NID	Not Important Deviation
PD	Protocol Deviation
PDHP	Protocol Deviation Handling Plan

PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File

8 CHANGES SINCE LAST REVISION

CT SOP version no 1.0

Main changes from LM SOP no. 2.04. Adapted to the wording of the clinical trial regulation no 536/2014. Recording of NID added.