1 PURPOSE

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe how to ensure good quality by adequate risk management throughout all phases of a clinical trial, from planning to publication.

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.

2 SCOPE

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

Quality management includes an adequate trial protocol, an expedient tool for data capture and processing, as well as a thorough risk evaluation and appropriate handling of the risks identified through all phases of the trial. A required part of the risk handling in clinical drug studies is the monitoring plan, which should reflect the risks identified for the trial.

3 RESPONSIBILITIES

Sponsor has an overall responsibility to implement a system to ensure quality in all phases of the trial according to this SOP. Sponsor should ensure all aspects of the trial are feasible. Unnecessary complexity should be avoided. The protocol, data capture system, monitoring plan and other trial documents should be clear, concise and consistent. This task is delegated to the coordinating investigator.

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.

4 PROCEDURES

4.1 Before study start

A well written protocol is the first step to ensure the quality of the trial, see SOP Protocol.

The protocol should take into account all processes and critical data to ensure the well-being of the trial participant and the reliability of the study results. Study specific procedures may also be required to complement the protocol e.g. on how to handle biological samples.

Next step of the quality management is to ensure an adequate data capture system is available for the study. A paper based tool is acceptable, but not recommended. See data collection tools for electronic data capture systems (eDCS) / eCRF (electronic Case Record Form). For single centre studies, the institution might have other eDCSs available.

Risk proportionate approaches in clinical trials provides recommendations especially concerning safety reporting, investigational medicinal product (IMP) traceability and accountability, monitoring and trial documentation. In short, the following adaptation could be considered based on a risk assessment included in the protocol:

- Selective recording and reporting of adverse events and/or adaptation to immediate reporting from the investigator to the sponsor for certain serious adverse events.
- Reduced accountability records for IMPs used as described in the Summary of product characteristics (SmPC).
- Reduced monitoring (see below)
- The content of the trial master file and Investigator's site file will follow the adaptations made for the trial. Worth noting is that the clinical study report may be absent as it is replaced by a medical journal publication (reporting of results in CTIS still applies), temperature monitoring and labelling may not be necessary, laboratory accreditation certificates and reference ranges may be omitted if the analyses do not provide critical information to the reliability of the trial results.

A risk assessment should be performed by the coordinating investigator, and should be conducted before the trial is initiated and thereafter on a regular basis throughout the trial. It is recommended that an interdisciplinary group of involved study personnel and support functions participate in the risk assessment. A useful template to be used for risk assessment is attached to this SOP; Risk Assessment Template. This template also includes an Organisational Overview.

The purpose of the risk assessment is to identify specific processes critical to ensure trial subject's protection and the integrity of the data to be collected in the trial. The risk assessment should also include an evaluation of the following parameters:

- Likelihood
- Consequence
- Risk for not detecting

The parameters should be graded into low, medium and high. Further, the assessment should also include a consideration whether the risk is acceptable or not, and if acceptable; an assessment of the need for threshold values, e.g. how much deviation / how many deviations can be accepted before certain measures or actions should be taken.

As an outcome of the risk assessment, coordinating investigator will decide upon different solutions and actions to be performed and by whom, to prevent or reduce the risk for events and deviations to occur. These should all be documented in the Risk Assessment Template.

Before the study is initiated, a Monitoring Plan for the study will be written. This should take into account the risk assessment already done and mitigate risks identified which can effectively be discovered and corrected by monitoring. Examples of risks that can be mitigated by monitoring is lack of adherence to protocol, inadequate consenting procedure, deviation in collection of primary and secondary endpoints or safety data, missing essential and required study documents and inappropriate facilities and equipment.

The risk assessment should take into account whether the clinical trial is a low-intervention trial, the objective and methodology of the trial and the degree of deviation of the intervention from normal clinical practice. This will again influence the monitoring plan.

4.2 Recruitment and delivery phase

A regular review of the risk assessment is required. This can be done annually, e.g. at the time for submitting the annual report through the Clinical Trial Information System (CTIS). A more frequent review may be required. The regular review should also include a check that previous solutions and actions agreed upon are completed accordingly. Any changes in the associated risk may influence e.g. the monitoring plan, the protocol or study conduct process.

All quality management activities should be documented and communicated to the concerned parties.

4.3 Close out phase

The quality management implemented for the trial together with important deviations should be taken into consideration when publishing the trial results.

5 NON-COMPLIANCE MANAGEMENT

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution. Protocol deviations should be reported according to the study protocol or the Protocol Deviation Handling plan.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- ICH Guideline for Good Clinical Practice (GCP) E6 (R2)
- Risk proportionate approaches in clinical trials

6.2 INTERNAL REFERENCES

7 ATTACHMENTS

- Risk Assessment Template
- Monitoring Plan

8 DEFINITIONS

- SOP Definitions.

Abbreviation	Term

CRO	Contract Research Organisation
CTIS	Clinical Trial Information System
eCRF	electronic Case Record Form
eDCS	electronic data capture systems
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure

9 CHANGES FROM PREVIOUS VERSION

CT SOP version no 1.0

Main changes from LM SOP No. 2.02. version nr. 3.1. Adapted to the wording of the clinical trial regulation no 536/2014 and to ”Risk proportionate approaches in clinical trials”.