

Guideline for a coordinated GCP-monitoring of clinical trials in the Nordic countries

Scope: The scope of this guideline is monitoring of academic clinical trials that are conducted in more than one Nordic country.

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NORM

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1 Introduction

In the Nordic countries GCP Units linked to hospitals and universities have a long standing tradition of working with monitoring and quality assurance regarding academic clinical trials conducted simultaneously in the Nordic countries. To strengthen the collaboration between the Nordic GCP Units a Nordic Monitoring Network (NORM) has been established. This guideline has been developed by NORM.

The aim of the guideline is to describe a coordinated approach to GCP monitoring of clinical trials within the Nordic countries. For trials conducted in more than one Nordic country the guideline will facilitate monitoring and improve the quality of the monitoring process of the specific trial.

2 Purpose

The aim of the guideline is to describe the prerequisites required for collaboration within the Nordic GCP Units specifically associated with the monitoring of academic trials.

In addition it will describe how the extent of the GCP monitoring is assessed, established and documented in a written monitoring plan.

3 Basis fundamental principles

Regulatory standards/ fundamental principles or standards

Legal context:

- The 'Clinical Trial Directive', [Directive 2001/20/EC](#)[☒]
- The 'GCP Directive' [Directive 2005/28/EC](#)[☒]

Relevant guidelines:

- ICH harmonised tripartite guideline for good clinical practice (ICH-GCP)
- ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155)
- EMA Reflection paper on risk based quality management in clinical trials, 18 November 2013

Definitions:

Clinical trial:

A clinical trial is an investigation of a medicinal product or a medical device in humans that requires compliance with ICH-GCP and ISO 14155 respectively.

Compliance with ICH-GCP or ISO 14155 may be relevant and requested in clinical investigations not including medicinal products or medical devices. In this context such clinical investigation will be regarded as a clinical trial.

Sponsor:

The sponsor of a clinical trial takes responsibility for the initiation and management, and/or financing of a clinical trial. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs) to ensure

that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

In this context the sponsor will mainly be represented by the academic organizations in one or more of the Nordic countries or an academic organization outside the Nordic countries.

National coordinating investigator/Nordic trial coordinator:

The sponsor may transfer sponsor related duties and functions to a national coordinating investigator in each Nordic country or a Nordic trial coordinator.

GCP Unit:

A GCP Unit is a public, non-commercial organization working within the field of monitoring and quality control of academic clinical trials in the Nordic countries. The employees, in this document called monitors, are educated and trained in the principles of GCP and have experience of monitoring academic clinical trials according to GCP regulations. The qualifications of the employees must be documented.

Coordinating GCP Unit (C-GCP Unit):

The coordinating GCP Unit is the unit that coordinates the monitoring of a specific trial. The coordinating unit can be the GCP Unit associated with the sponsor's organization or it can be a GCP Unit appointed by the sponsor.

Coordinating monitor:

The monitor responsible for the trial in the C-GCP Unit is referred to as the coordinating monitor in this document.

National coordinating GCP Unit (NC-GCP Unit):

If several centers from the same country are participating in a trial, a NC-GCP Unit can be used. The NC-GCP Unit is the unit that coordinates monitoring of a specific trial within a country. The NC-GCP Unit is associated with the national coordinating investigator's organization.

Nordic Monitoring Network (NORM):

NORM is an abbreviation for the Nordic Monitoring Network and is a network of monitors employed by GCP Units. A description of the organization and a list of GCP Units participating in NORM are to be found on the NRI webpage <http://www.nordicnetworks.org/>

4 Description

The main purpose of NORM is to develop guidelines and coordinate monitoring of clinical trials initiated by a sponsor representing an academic organization in one or more of the Nordic countries.

Nordic GCP Units may be requested to monitor clinical trials where the sponsor represents an organization outside the Nordic countries. Individual sponsors make arrangements concerning monitoring directly with the GCP Units, or arrangements may be delegated to a Nordic trial coordinator, or a national coordinating investigator in each Nordic country. When relevant, the monitoring of a trial in the Nordic countries can be coordinated according to the principles in this guideline.

4.1 Monitoring contract

The monitoring contract is an agreement between the sponsor and each participating GCP Unit or between the national coordinating investigator and the GCP Units. The monitoring contract outlines the specific duties concerned with monitoring and quality assurance, which are delegated to the GCP Units according to the monitoring plan. The monitoring contract also describes the financial agreement between each GCP Unit and the sponsor/national coordinating investigator.

The contract should be signed by the sponsor/national coordinating investigator and the GCP Unit prior to inclusion of study participants at the actual sites.

4.2 Monitoring plan

The monitoring plan describes in detail the extent of the monitoring of a clinical trial. The final monitoring plan has to be considered as a mutual agreement and should be approved by the sponsor and the C-GCP Unit if not otherwise decided by the sponsor. A national appendix should be approved by the sponsor, national coordinating investigator and the NC-GCP Unit if not otherwise decided by the sponsor.

The monitoring plan should be ready before inclusion of the first trial subject.

The Sponsor is responsible for the monitoring and the Monitoring plan may be provided by the sponsor to the C-GCP unit. If not, the C-GCP Unit may prepare the monitoring plan in collaboration with the sponsor according to a risk based assessment.

If a sponsor or national coordinating investigator has developed a monitoring plan without involving the GCP Unit, the GCP monitor is responsible for assessing whether this monitoring plan is consistent with the usual expectations of monitoring of drug trials in the Nordic countries. If not, the GCP-unit is free to refuse the monitoring plan.

4.2.1 Risk assessment

The aim of risk assessment is to identify the weak links and critical processes of the trial before initiation of the trial in order to be able to establish preventing procedures.

Every risk evaluation must be related to protection of the rights, safety, and well-being of trial subjects and the credibility of the results of the clinical trials.

When performing risk assessment, a combination of assessors should be involved including, if possible:

- persons with knowledge in the respective medical indication and research field
- persons with knowledge regarding the clinical procedures at the sites
- pharmacist, radiologist, biochemist, statisticians and other specialists when relevant

At least the Coordinating monitor should be trained on performing risk assessments.

It is important to consider how data are generated, collected, registered, and reported in the risk assessment process.

Already established quality assurance systems like laboratory guidelines, temperature control of medication storage rooms, central monitoring etc. should be taken into account.

In multicentre trials the risk assessment shall comprise all involved sites. Therefore, when feasible, discussions between the C-GCP Unit and GCP Units expected to participate in the monitoring of the trial should be undertaken.

The risk assessment is primarily done based on the protocol but CRF, study SOPs, knowledge of the sites, and data flow should be included if possible.

When a risk is identified, the probability and severity of the consequences should be assessed.

When evaluating the risk of the trial, the C-GCP Unit must make a risk assessment involving following items: Study organization and governance, training, trial subject's rights and safety, data, protocol procedures, Investigational medicine product, safety management and impact. The risk assessment must be documented. The C-GCP Unit can make use of and fill out **Appendix 7.1, Risk Assessment Tool (RAT)**. The document should have a version and a date.

The risk assessment must be completed by C-GCP Unit covering the sponsor-investigator center and sponsor related items and will be distributed to the NC-GCP Units.

The NC-GCP Unit is responsible for evaluating if the risk assessment is applicable in home country. If not, the NC-GCP Unit must report differences back to the C-GCP Unit. If necessary, a revised risk assessment is filled out by the C-GCP Unit and distributed to all participating GCP Units.

All GCP Units are responsible for evaluating if the risk assessment is applicable in a specific center. If not, the GCP Unit must report back to the NC-GCP Unit so that local issues can be described in the appendix to the monitoring plan.

The RAT consists of eight columns.

The first column describes the general topics to be evaluated for every trial. In certain projects, there may be areas that do not fall within the eight areas but still may carry a risk for trial subjects' safety and/or rights or the data quality. These areas can be mentioned under "Other".

The second column includes sub-headings that often must be evaluated. This column should be adapted to the specific trial.

In the third column the risk for trial subjects' safety and/or rights or the data quality in the trial is recorded with a correlation to the sub-headings in column two (e.g. 2.1 is the first risk correlated to study staff and training). If possible, the cause of the risk should be identified.

The fourth column describes the likelihood of errors occurring, given existing risk controls.

The fifth column describes the impact of such errors on human subject protection and data integrity

The sixth column describes the extent to which such errors would be detectable.

In the seventh column the assessors should identify whether the risk can be accepted or not and/or how it should be reduced (through mitigating actions). Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

The eighth column describes which process controls the risk.

The use of the different columns will vary according to the timing of the risk assessment. Before study start, all columns should be reviewed.

To evaluate whether there is a risk or not and whether a risk has been handled or not, **Appendix 7.2, Considerations of possible risk indicators and proposal for monitoring strategy** can be used. The contents of Appendix 7.2 are solely examples of risk indicators. Some items may be mentioned twice because of the different perspective: protection of the rights, safety and well-being of trial subjects or the credibility of the results of the clinical trials.

When it has been established that there is a relevant risk, it should be assessed whether this could be reduced, e.g. by elaborating a SOP, carrying out documented training of relevant staff or entering into contracts with other collaborators (e.g. by data transfer of primary effect parameters).

If the risk regarding any item is expected to be reduced, monitoring of that particular area should only be done randomly to verify whether this is in fact the case. For instance, the item should only be checked for the first few included trial subjects.

If the risk can't be reduced, the monitoring plan should describe how to oversee and ensure that the trial is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements. In Appendix 7.2 examples of monitoring strategy for each item are suggested.

4.2.2 Preparation

Appendix 7.3, Template for monitoring plan should be used as a template for the monitoring plan. The contents should be adjusted for the individual trial. **Blue-coloured** text must always be evaluated and perhaps rephrased. **Red-coloured** text must be deleted as this is solely a matter of guidance.

If there are any specific national requirements that should be followed an appendix for each country must be completed. Any site specific requirements must be described in the national appendix.

The monitoring plan should be phrased in such a way that it is apparent how and when the monitor shall carry out the monitoring as well as what is to be monitored. For instance, there may be matters to be monitored at the initiation visit and matters to be monitored at sponsor' site after the completion of the trial.

4.2.3 Evaluation

In case of important changes such as protocol amendments or changes in staff an evaluation of the consequence of these changes for the existing risk assessment must be made. The evaluation shall be documented by correspondence with the sponsor. If relevant, the monitoring plan should be revised. The monitoring plan should also be revised if the monitoring reveals fewer or more deviations than expected.

4.3 Standard Operating Procedures and report templates

Monitoring should be performed according to GCP requirements and according to standard operating procedures (SOPs) which have been agreed upon. SOPs may be the local SOPs of each GCP Unit or specific SOPs chosen to be used. The decision to use local or specific SOPs including report templates should be documented in the monitoring contract.

4.4 Coordinating of monitoring

Monitoring of a clinical trial is the responsibility of the sponsor. Sponsors may transfer specific duties related to the organization of the monitoring to the C-GCP Unit. The C-GCP Unit will be the principle liaison between the sponsor and the GCP Units. The delegated duties should be clearly agreed upon and documented between the C-GCP Unit and sponsor.

Coordination may include some of the following tasks:

4.4.1 Identification of GCP Units to participate in the trial

A list of appropriate GCP Units can be provided by the C-GCP Unit to the sponsor. The sponsor chooses suitable GCP Units which can be contacted either personally or through a national coordinating investigator.

The C-GCP Unit can also assist in identifying relevant NC-GCP Units.

4.4.2 Distribution of documents and correspondence

The C-GCP Unit can assist with the distribution of documents and correspondence from sponsor to relevant GCP Units. The G-GCP Unit can distribute:

- trial documents to participating GCP Units
- trial related correspondence to participating GCP Units

4.4.3 Procedures to assure a uniform monitoring

C-GCP Unit can contribute to uniformity of trial monitoring by:

- informing the other GCP Units about issues relevant for monitoring of the trial
- making sure that questions and issues regarding monitoring from other GCP Units are answered (by sponsor if relevant)
- arranging meetings/telephone conferences-meetings/discussions concerning monitoring related questions and issues

5 Storage

This document can be stored in each GCP Unit according to procedures for filing documents included in the GCP Units quality system; it can also be accessed on the webpage for NRI.

6 Log of changes

Version	Date	Reason for change
Version 1	01.03.2014	First version
Version 2	20.11.2014	New definitions. Revision of 4.2. Monitoring plan. Template and Risk assessment were added
Version 3	01.04.2015	Information about members of monitoring plan (MP) group added 4.4.2: Template for monitoring plan must be used changed to Template for monitoring plan should be used 4.4.3: Procedures to assure a uniform monitoring have been changed
Version 4	15.10.2015	Clarification and admin update. Definition for a Nordic trial coordinator added 4.2: The monitoring plan shall be ready before inclusion of the first trial subject changed to a monitoring plan should be ready before inclusion on of the first trial subject Added: The GCP-unit can refuse a monitoring plan developed by sponsor without involving the GCP Unit New column in the RAT

7 Appendices

7.1 Risk Assessment Tool

Protocol							
EUdraCT number							
Sponsor							
Centers evaluated							
Assessors involved							
Date and version of risk assessment							
Topics	Items (to be adapted)	CONSIDERATION OF POSSIBLE RISKS	LIKELIHOOD	IMPACT	DETECTABILITY	MANAGEMENT STRATEGY FOR MITIGATION OF RISK (protocol, agreements monitoring plans, SOPs, training or monitoring etc.)	CONTROL BY monitoring
1 Study organisation and governance	1.1. Communication plan						
	1.2. Financial Resources						
	1.3. Agreement						
	1.4. SOP and Quality systems						
	1.5. Trial Master File						
	Other						

2	Training	2.1 Study staff						
		2.2 Other						
3	Trial subjects rights and safety	3.1 Informed consent						
		3.2 Safety measurements/Examinations						
		3.3 In-/exclusion criteria						
		3.4 Withdrawal / drop out						
		3.5 Concomitant medication						
		3.6 Contraindicated medication						
		3.7 Degree of intervention						
		3.8 Other						
4	Data	4.1 Data protection						
		4.2 Data capture						
		4.3 Recording data						
		4.4 Data validation						
		4.5 Database lock						
		4.6 Other						
5	Protocol procedures	5.1 Main endpoints / variables						
		5.2 Protocol specified procedures (complexity)						
		5.3 Research biobank						
		5.4 Other						

6	Study Drug/ IMP	6.1 Knowledge of Study Drug						
		6.2 Randomization						
		6.3 Manufacturing 6.3.1 Labelling 6.3.2 Blinding						
		6.4 Handling of study drug at site 6.4.1 Storage 6.4.2 Administration						
		6.5 Compliance and accountability of study drug						
		6.6 Other						
7	Safety managemen t	7.1 Registration and report of AEs /ARs						
		7.2 Registration and report of SAE, SAR, SUSAR						
		7.3 Report for authorities						
		7.4 Other						
8	Impact	8.1 Impact of study results						
		8.2 Other						
9	Other	9.1 Anything else which is important in this study						

7.2 Considerations of possible risk indicators and proposal for monitoring strategy

1. Study organization and governance

1.1 Communication plan

Considerations of possible risk indicators

- Lacking communication plan
- Lacking coordination (sponsor or coordinating investigator) in case of complex trials with many involved parties
- Trial with many participating sites/involved parties
- Trial in which trial documents are often revised
- Lacking documentation of important correspondence
- No investigator meeting at upstart or during the trial
- Lack of interest in the cooperation with the GCP unit, including lack of securing that the GCP monitor is provided sufficient insight into the trial/the quality assurance procedures of the department
- Participation of foreign sites from which – among other things – separate ethics committee approvals need to be obtained giving rise to specific measures

Strategy for monitoring

- Check that the participating sites have received relevant documents/information from sponsor (review of Trial Master File)
- Check that the participating sites will distribute relevant information to relevant project staff at the site (review of Trial Master File)
- Individual monitoring visit at sponsor's site once annually
- Check that sponsor responds to questions/input he/she receives from participating sites (review of Trial Master File)

1.2 Financial resources

Considerations of possible risk indicators

- Lack of budget to cover costs such as study nurses, study coordinators, monitoring, data management etc.
- Lack of budget to cover cost for study procedures such as lab, pathology, imaging, IMP manufacturing and handling

1.3 Agreements

Considerations of possible risk indicators

- The responsibility for monitoring is delegated to the National Coordinating Investigator
- Essential study contributors have not been asked/agreed to dedicate required resources into the study
- No agreements has been done with qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses and to prepare the trial reports

Strategy for monitoring

- Check that agreements are in place
- Check for protocol compliance

1.4 SOP and Quality systems

Considerations of possible risk indicators

- Inadequate document management/versioning
- Insufficient SOPs for key procedures in the trial
- Inadequate responses reaction to deviations from established quality assurance systems, e.g. Inadequate adherence to SOPs
- Inadequate follow-up with unresolved issues detected at monitoring or at audit
- Inadequate implementation of new legislation for clinical trials in the quality assurance department
- Lack of Data Monitoring Committee
- Lack of working procedures for the Data Monitoring Committee

Strategy for monitoring

- Check that sites make use of the current project documents
- Random check that relevant SOPs are complied with

1.5 Trial Master File

Considerations of possible risk indicators

- The Trial Master File is assembled and maintained by the site, and with a significant change of project staff, there is an increased risk of inadequate documentation or that documents are out of date
- Inadequate update of the Trial Master File may result in an insufficient overview of trial status and activities with a risk of inadequate compliance with GCP
- When several sites participate there is a risk that certain sites do not receive additional relevant documents to be filed in the Trial Master Files locally

Strategy for monitoring

- Check that the Trial Master File is updated one or several times annually or as needed
- Check that sponsor will distribute relevant and revised documents to the other participating sites

2. Training

2.1 Study staff

Considerations of possible risk indicators

- Lack or insufficient qualifications for project staff carrying out trial-related tasks, e.g. obtaining of consent, inclusion, registration of events and adverse reactions as well as data registration.
- Lack of delegation of trial-specific tasks in the trial
- Considerable change of staff at the site or unexperienced staff in relation to knowledge on requirements for clinical trials
- Lack or insufficient training of staff to be involved in trials
- Inappropriate organization at the site
- Lacking resources at the site in relation to the amount of tasks required by the trial
- Delegation of tasks to a profession not normally performing this type of tasks, e.g. a nurse informing patients about the trial by herself
- One site included in the trial later than the others and therefore at risk of a lack of information

- Protocol treatment and data collection taking place at more than one department

Strategy for monitoring

- Check that only project staff who have been delegated the task will carry these tasks
- Check that project staff has relevant and sufficient qualifications at the time of task delegation
- Check that tasks delegated to a profession not normally carrying out this task, is done in accordance with approved documents
- Check that protocol is followed and that all data are recorded for the first few patients at each site.

3. Trial subjects' rights and general safety

3.1 Informed consent

Considerations of possible risk indicators

- Information procedure not clearly described in the protocol or other accessible places for all sites
- Trials with children where both parents should consent timely or where documentation for one-parent authorization should be available
- In case of trials with incompetent persons if there is no training of staff and procedures available to secure that consent is obtained if the trial subject regains his competence to act.

Strategy for monitoring

- It shall be checked that no protocol-specific procedures have taken place before informed consent is obtained
- It shall be checked for all trial subjects/the first X trial subjects that informed consent has been obtained only by persons delegated for this
- It shall be checked for all trial subjects/the first X trial subjects that correctly completed consent forms are in place
- It shall be checked that delivery of oral and written information as well as the trial subject's consent have been correctly recorded in the medical record for all included/for the first X trial subjects
- It shall be checked for all trial subjects that in case of acute trials, consent is available from both trial guardian and acting consent as well as from the trial subject if he/she has regained his/her competence to act.
- It shall be checked for all trial subjects that in trials with incompetent persons, acting consent and consent from the trial subject, if he/she has regained his/her competence to act, should be available
- It shall be checked for all trial subjects that in trials with under-age children, written consent is in place from both parents in a timely manner or that documentation for one-parent authorization is available

3.2 Safety measurements/examinations

Considerations of possible risk indicators

- The examination is not routine at the department
- The examination is not a routine task for the trial staff
- There seems to be no clear procedure for carrying out the examination
- Unclear procedure regarding when and how the analysis should be done
- Unclear procedure regarding evaluation of the test result

Strategy for monitoring

- Check that the examination has been done at the correct time according to protocol/SOP and that staff authorised for this have evaluated the result

- Check that the analysis has been done at correct time according to protocol/SOP and that persons authorised for this have evaluated the result

3.3 Inclusion and exclusion criteria

Considerations of possible risk indicators

- In- and/or exclusion criteria require protocol-specific acts that deviate from normal practice and require that these are carried out by qualified staff
- Criteria requiring a professional assessment and where this assessment neither appears in the medical record data nor in old notes/records from other departments/hospitals, and when it cannot be verified that the outcome of the professional assessment is correct

Strategy for monitoring

- All in- and exclusion criteria for all trial subjects shall be checked
- Selected in- and exclusion criteria for all trial subjects shall be checked
- It shall be checked that inclusion of trial subjects has solely been done by qualified staff delegated this task

3.4 Withdrawal / Drop-out

Considerations of possible risk indicators

- It is not routinely checked by the staff whether criteria for withdrawal have taken place
- Conditions of importance for trial subject safety are not checked routinely (e.g., there are no procedures to secure that safety blood tests are performed and evaluated)

Strategy for monitoring

- It is checked for all trial subjects/selected trial subjects during review of the medical record that fulfilling of selected withdrawal criteria have led to withdrawal of trial subjects

3.5 Concomitant medication

Considerations of possible risk indicators

- The protocol-specific treatment deviates from and replaces the normal treatment of the department
- If concomitant treatment is not administered, trial subjects safety is at risk
- If concomitant treatment is not administered, the accuracy of the trial result is at risk of being influenced
- Prohibited concomitant medication

Strategy for monitoring

- It will be checked at review of medical records for all/X trial subjects from inclusion to drop-out of the trial whether concomitant medication is administered according to protocol

3.6 Contra-indicated medication

Considerations of possible risk indicators

- Contra-indicated medication that does not pose an unimportant safety risk for the trial subject
- Contra-indicated medication that may affect the trial results

Strategy for monitoring

- It will be checked at review of medical records for all/X trial subjects from inclusion to exclusion of the trial whether any contra-indicated medication has been administered

3.7 Degree of intervention (apart from IMP))

Considerations of possible risk indicators

- Inclusion of non-therapeutic interventions not included in routine care e.g. biopsies, extra radiological examinations
- Demands of extensive changes of behaviour for the patient compared to routine care e.g. diaries, questionnaires or several extra visits

Strategy for monitoring

- If possible, check that the subjects have been given written and verbal information about the non-therapeutically aspect of the intervention and the possible risks associated with the trial
- Check that all patients have been informed by qualified staff delegated to that task

4. Data

4.1 Data protection

Additional requirements if data handling is outsourced to an external data handling unit (DHU)

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
Data handling unit	e.g. external data handling unit	Agreement with data handler in place according to regulations
Approval of DHU	e.g. systems and procedures	DHU should be audited regarding applicable requirements regarding procedures and systems.

Elements of the risk assessment below may be redundant if an external data handling unit is performing the tasks. The procedures should be in place at the contracted DHU.

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
Unauthorized access	e.g. unauthorized or untrained persons able to access data, CRF	Procedures and systems in place to prevent unauthorized persons to access data.
Delegation of tasks	e.g. data entry and verification	Procedures and documentation of delegation of tasks in place
Protection and confidentiality of patient data	e.g. person-identifiable data in the CRF/ Database	Data stored and distributed according to regulations
Loss of data	e.g. unintended deletion of data	Validated back-up procedures
Data collected from source documents containing other data than required by the protocol	e.g. blood sample results sent to sponsor as a copy	Copies of source documents should only comprises necessary information
Data filing	e.g. hardware platform or software used to store data.	Data filing procedures should be in place

	Data should be retrieved in their original form during the filing period	<i>-check that the electronic data is retrievable</i>
Subject identification code	e.g. lack of unambiguous subject identification code	Consistent subject identification code for all data sources
Confidential documentation	e.g. patient identification list not stored in a locked filing-cabinet.	Procedures and facilities in place to ensure safe storage of confidential documents. <i>-Check that source data, identification list and other documents with personal information is stored safely</i>

4.2 Data capture

If only “CRF” is stated it relates to both paper CRF (pCRF) and electronic CRF (eCRF)

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
According to protocol	e.g. the CRF do not capture all data points or more than the required data points according to protocol	QC of CRF, protocol and source data listing. Procedures and systems in place to ensure QC of CRF design
According to SAP	e.g. the CRF do not capture all data points or more than the data points required to perform the analyses described in the SAP	QC of CRF, SAP and source data listing. Procedures and systems in place to ensure QC of CRF design
Recording of deviations	e.g. recording of protocol deviations	The CRF should be designed to capture deviations
CRF logic	e.g. it is not clear whether AE registration should be done in connection with the current or subsequent cure	The CRF should be designed to capture data logically and consistent and avoid redundant data capture
Changes to CRF	e.g. amendments to protocol requiring changes to the CRF or data capture procedures	Procedures in place to track changes to CRF or other data capture and the implementation of the changes at site. <i>-Check change log</i>

4.3 Recording data

If only “CRF” is stated it relates to both paper CRF (pCRF) and electronic CRF (eCRF)

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
Qualified personnel	e.g. project staff carrying out data registration are not sufficiently qualified	Procedures in place to ensure training Study related tasks should only be carried out by trained and authorized personnel

Many persons involved in the data registration	e.g. more than one person authorized to sign the CRF or capture study related data	Only project personnel authorized for it should perform study related tasks and the delegation log should be completed. <i>-Check delegation log</i>
Altering of data	e.g. corrections of data in the pCRF or no audit trail in the eCRF	Procedures should be in place for documentation of changes to the pCRF. A visible audit trail should be integrated in the eCRF. <i>-Check the audit trail</i>
Signed data assessment	e.g. assessment whether an AE is related to the trial medication or not should be signed off	CRF should be designed to capture the signature of the person responsible for the additional assessment of signed data
CRF not available	e.g. CRF – used for registration of source data – are not available in connection with the execution of the trial activity	Procedures should be in place to ensure correct data capture during all study related tasks. E.g. paper copy available
Central assessment of data	e.g. The examination or assessment of data from an examination in a multicentre trial, e.g. an x-ray image, takes place at sponsor's site.	Procedures should be in place to ensure copies or originals remain at site.
Protocol compliance	e.g. all mandatory data recorded	<i>-Monitoring that all data to be registered according to the protocol are registered for the first x number of patients</i>
Mapping of source data	e.g. information could be retrieved from the general practitioner, other health care institutions or external laboratory.	Sources of all data required according to protocol should be identified and listed. Authorized personnel for data capture and assessment should be allocated. <i>-Check listing of source data and were to locate all variables</i>
Source data	e.g. CRF is not source data	Source data verification should be done for the primary effect parameter for all included trial subjects <i>-Source data verification of all registered data, typically for the first X number of patients.</i>
Data transfer between two electronic systems	e.g. lab data to eCRF	Procedures in place to ensure QC of data transfer
Data transfer from paper to electronically systems	e.g. pCRF to eCRF	Procedures in place to ensure continuous data entry, data verification and/or data control.

4.4 Data validation

If only “CRF” is stated it relates to both paper CRF (pCRF) and electronic CRF (eCRF)

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
Data control	e.g. consistency and logical checks of the electronic data	Agreement should be in place to ensure QC of data
Data queries	e.g. query handling	Procedures in place to ensure query handling. -Check disproportionately many queries -Check corrections made based on queries

4.5 Database lock

If only “CRF” is stated it relates to both paper CRF (pCRF) and electronic CRF (eCRF)

Considerations of possible risk indicators		Risk control (Mitigation and/ or acceptance)
SAE	e.g. if only paper copies of SAE forms available	Procedure in place to ensure copies of all SAE forms sent to data handling unit by paper or electronically -Check SAE log
SAE reconciliation	e.g. no external data handling unit responsible for SAE reconciliation	Procedures in place to ensure SAE reconciliation and QC of the SAE process
Note to file	e.g. if only paper copies of Note to files available	Procedure in place to ensure copies of all Note to files sent to data handling unit by paper or electronically -Check NTF log
Randomization/blinding	e.g. protocol violation through study drug and/or handling of randomization/blinding	Procedures in place to ensure compliance to protocol with regards to randomization/blinding. -Check randomization envelopes
Database lock	e.g. no external data handling unit responsible for database lock	Procedures in place to ensure database lock according to regulations

5. Protocol procedures

5.1 Main endpoints /variables

Considerations of possible risk indicators

- Examination of primary effect parameter or other important parameter takes place at another department where the examination is not routine
- The examination is not routine at the department

- The examination is not a routine task for the trial staff
- There is no clear procedure available for carrying out the examination (e.g. physical examination)
- The trial is a multicentre trial in which data from several sites are to be compared for any examination. Measures that will ensure that data are comparable (same equipment, method of measurement, use of internal standard) are not available
- There are no quality assurance procedures available, including calibration procedures for equipment used for the examination
- Generation of data takes place in a subjective manner thereby risking individual difference in assessment of effect
- The trial is a multicentre trial in which data from several sites are to be compared for an analysis and no measures have been taken to secure that data are comparable (same equipment, method of measurement, use of internal standard)

Strategy for monitoring

- A visit at another department in connection with initiation and hereafter e.g. once annually
- Check that the examination has been done at the correct time according to protocol/SOP and by persons authorised for this
- Check that the sample has been drawn and analysed according to protocol and is correctly registered in CRF

5.2 Protocol specific procedures

Protocol-specific examinations could e.g. be examinations that are done to assess whether the person in question is suitable for inclusion in the trial

Protocol-specific analyses are e.g. analyses that are done to assess whether the person is suitable for inclusion in the trial. The analyses could be routine analyses

Considerations of possible risk indicators

- The examination is not routine at the department
- The examination is not a routine task for the trial staff
- There is no clear procedure for carrying out the examination (e.g. physical examination)
- Unclear procedure for sampling and analysis of sample
- The analysis is a primary effect parameter or other important parameter
- The analysis is not standard but established in connection with the trial
- Analysis of the sample is not a routine analysis

Strategy for monitoring

- Check that the examination has been done at the correct time according to protocol/SOP and by staff authorised for this
- Check that the analysis has been done and analysed according to protocol and correctly registered in CRF
- A visit at the laboratory in connection with initiation and thereafter e.g. once annually
- Check that there are method description and documentation available regarding quality control for non-routine analyses

5.3 Research biobank

Considerations of possible risk indicators

- Unclear procedure for sampling, handling, labelling and/or storage of samples
- Unclear indication of when the research biobank samples should be analysed

- Analysis of the research biobank sample is not a routine analysis

Strategy for monitoring

- Check that records of stored samples are being kept
- Check that samples in research biobank have been drawn, handled, labelled and stored correctly
- Check that method description and documentation for quality control for non-routine analyses are available
- Check that the test result for research biobank samples has been registered correctly

6. Study drug/IMP

6.1 Knowledge of study drug

Considerations of possible risk indicators

- Lack of knowledge about trial medication, including unsafe side effect profile making up a risk in relation to trial subjects' safety
- Non-marketed trial medication, phase I-III
- Marketed trial medication used for a new indication, new doses and/or route of administration
- Use of advanced therapies (somatic cell therapy, gene therapy or tissue engineering)

Strategy for monitoring

- See strategy under item 7. Collection and reporting of AE/AR
- If possible, check that the subject have been given written and verbal information about the non-therapeutically aspect of the intervention and the possible risks associated, or the consequences of the use of advanced therapies.

6.2 Randomization

Considerations of possible risk indicators

- Deficient procedure for production of randomisation list, e.g. a randomization list is elaborated by project staff or by use of an insecure method, like e.g. throw of the dice
- Complex randomisation procedure e.g. comprising of several treatment arms and stratifications
- Deficient method for allocation of trial medication, e.g. doubt whether the allocation is blinded
- Allocation takes place at the site by direct reading of randomization lists or envelopes

Strategy for monitoring

- To check, at initiation, that an unambiguous procedure for production of randomisation list is available. If necessary, an unblinded monitor could check that randomization has been done according to the protocol
- To check, at initiation, that an unambiguous procedure for randomisation is available
- To check that trial subjects will be treated according to randomization
- To check, at monitoring (if possible by unblinded monitor), that allocation has been done correctly and is documented

6.3 Manufacturing, labelling - blinding

Considerations of possible risk indicators

- The trial medication is manufactured from scratch by hospital pharmacy, Nuclear medicine and PET center or other equivalent manufacturer

- The trial medication is a marketed drug that is modified e.g. in connection with blinding
- The trial medication shall be up-titrated or manufactured in different concentrations
- The trial medication is a marketed drug that shall be repacked
- The trial medication has a short durability for which reason manufacturing must take place with short intervals
- Distribution of trial medication is complex, e.g. that distribution takes place to various sites
- The trial medication is labelled by staff at the site
- The trial medication is manufactured from scratch or repacked in new container on which the label should comprise all details from appendix 13
- During the trial, a need for additional labelling may arise, e.g. in connection with prolonged durability
- Parts of the staff (e.g. anaesthesiologist or surgical nurse) are not blinded
- Trial treatment appears from the medical record (e.g. x-ray images)
- Unsafe method of packaging and/or labelling making it possible to break the blind
- Trial medications are administered in a way making it possible to break the blind
- Occurrence of effect and/or side effects making it possible to break the blind
- Influence on laboratory results or other, making it possible to break the blind

Strategy for monitoring

- A visit to the manufacturer in connection with initiation and thereafter e.g. once annually
- At initiation, it should be checked that a cooperation agreement is available clearly describing manufacturer's tasks in the trial
- At initiation, it should be checked that a clear procedure for labelling carried out by staff at the site is available
- At initiation and monitoring, it should be checked that documentation for labelling carried out by staff at the site is available
- At initiation and monitoring, it should be checked that labelling is done by trained staff
- At initiation, it should be checked that a label with correct information is available in Trial Master File
- Check that correct labelling of trial medication for the first X trial subjects is done
- To check, at initiation, that procedures are available to prevent that the blind is broken for trial subject or project staff
- To check, at initiation, the trial medication and ensure that the blind cannot be broken by a look at the container or label
- To check, at initiation, that a procedure for evaluation of data is available securing that the blind is not broken unintentionally
- To check that the code is not broken unintentionally during the trial

6.4 Handling of study drug at the site

Considerations of possible risk indicators

- There are specific requirements for storage of trial medication, e.g. cold storage
- The trial medication is to be finally manufactured at the site
- The trial medication has a short durability

Strategy for monitoring

- At initiation, it should be checked that a clear-cut procedure for handling of trial medication is available
- At monitoring, it should be checked that handling of trial medication is done by trained staff
- At monitoring, it should be checked that documentation for handling is available

- At monitoring, it should be randomly checked that correct storage of trial medication for supply and returned trial medication is done

6.5 Administration

Considerations of possible risk indicators

- Complex administration of trial medication
- Complex titration of dosage
- Several criteria giving rise to dose adjustments and/or discontinuation of trial medication

Strategy for monitoring

- To check, at monitoring, that trial medication is administered correctly

6.6 Compliance and accountability of study drug

Considerations of possible risk indicators

- Inadequate procedures for drug accountability, both at a general level and at trial subject level
- Inadequate procedures for securing compliance in the trial (procedures could be diary, determinations of concentrations, counting of returned trial medication)

Strategy for monitoring

- Check of overall drug accountability at site
- Check of drug accountability at trial subject level (for all or some of the trial subjects)
- Check of compliance

7. Safety management

7.1 Registration and report of AEs/ARs

Considerations of possible risk indicators

- There is no clear procedure by which AEs should be recorded and reported
- It has not been adequately and unambiguously described how AE should be collected and registered
- Typically, the trial subjects present with many baseline symptoms thereby risking error-/over registration of AE (is particularly relevant if side effect profile is primary endpoint)
- There is no awareness of collection of AE as these are not expected
- There are no clear procedures for evaluation and registration of related/non-related
- Contact with the trial subject is not managed by project staff but by other department staff
- The primary aim of the trial is the determination of MTD (Minimum Tolerated Dose) and DLT (Dose Limiting Toxicity)

Strategy for monitoring

- Medical records and perhaps patient diaries should be reviewed for all/X trial subjects from inclusion to exclusion of the trial in order to check whether registration and reporting of AE is complete
- It will be checked that AE have been evaluated by persons authorized for this
- It will be checked that baseline symptoms are taken into account at data registration/data entry

7.2 Registration and report of SAE/SAR/SUSAR

Considerations of possible risk indicators

- There is no clear procedure for which SAEs should be recorded and reported
- Practical procedure regarding reporting of SAE is vague
- SAE chart is not an appropriately designed
- Sponsor is not a regular visitor in the department
- The trial subjects will typically be hospitalized at their local hospital and not at the site, thereby increasing the risk of delayed reporting and underreporting of SAE
- Many sites and/or foreign sites are involved, thereby risk of lack of registration and reporting
- Typically, the trial subjects have been hospitalized many times, thereby risk of inadequate attention in the department that these should be registered as SAE
- Some SAE are exempted from immediate reporting, thereby risk that these are not reported to sponsor

Strategy for monitoring

- Medical records will be reviewed for all/X trial subjects from inclusion to exclusion of the trial in order to check whether registration and reporting of SAE is complete and timely
- It will be checked that all SAE reported by sites have been received and assessed timely by sponsor

7.3 Reports for authorities

Considerations of possible risk indicators

- There are no written procedures for safety reporting
- Many sites and/or foreign sites are involved, thereby risk of inadequate registration and reporting
- Some SAE are exempted from immediate reporting, thereby risk that these are not included in the annual safety assessment

Strategy for monitoring

- It will be checked that sponsor systematically collect and register SAE from all sites
- It will be checked that all SUSAR have been reported in a timely manner to applicable Authorities and Ethics Committees and subsequently to investigators
- There will be a random check that SAE/SAR, exempted from immediate reporting, are included in the annual safety report

8. Other

8.1 Impact of study results

Considerations of possible risk indicators

- The outcome off the trial will be the new standard treatment in many hospitals

Strategy for monitoring

- Close monitoring

7.3 Template for monitoring plan

Monitoring plan

1. Protocol title and identification number

Protocol title and version:

EudraCT number:

2. Monitoring conditions

The monitoring plan is based on the guideline for coordinated GCP-monitoring of clinical trials in the Nordic countries ([version 2/xx-xx-201x](#)), the study protocol [xxxxxx](#) and risk-based assessment [xxxxxx](#) and has been written in cooperation with the sponsor.

The actual SOP or SOP's for the monitoring process is stated in each national appendix or in the agreement or contract.

The monitoring plan describes the extent of the monitoring activities which will be performed by national monitors in each country.

Additional national requirements for each participating Nordic country are described by the [sponsor/national coordinating investigator](#) in the [appendix 1](#). **If more than one country has national requirements then make one appendix pr country.**

3. Monitoring activities

A combination of on-site and centralized monitoring activities may be appropriate. The rationale for the chosen monitoring strategy should be described.

3.1. Initiation

An initiation visit will take place at each site before the enrolment of study subject can begin.

When all requirements at a site are fulfilled, the sponsor will be noticed that the site is ready to start the inclusion (in the initiation report or in other applicable documentation).

If any discrepancies from the initiation visit take place the reason and extent will be described here or in the appendix 1 for additional national requirements and site-specific conditions.

Add specific parts that should be checked at the initiation visits if applicable or state details in the additional national appendix 1.

If an initiation visit will take place in the sponsors organization or at national coordinating investigator before the initiation visits at sites can start it should be described.

3.2 During the study

The first monitoring visit at each site should be performed [after enrolment of xx study subjects/ after xx study subjects has performed the first evaluation/ after xx study subjects has performed xx visits](#). **The first visit, at each site, will usually take place early after enrolment of the first study subject but the time should be purposeful and carefully evaluated according to the risk-based assessment.**

Thereafter monitoring visits at each site will be performed at regular basis according to the

agreement, inclusion rate, the risk-based assessment and dependent on findings from previous visits.

A minimum of one contact (by e-mail or telephone) or visit per year to each site is required.

3.3 Close-out visit

After the last study subject has performed the last visit a close-out monitoring visit should take place at each site. The close-out visit at each site can be combined with monitoring if applicable.

If a close-out visit will take place in the sponsors organization or at national coordinating investigator at the end of the study it should be described. For studies with a long follow-up a close-out visit might be undertaken before the follow-up data are collected.

Add specific parts that should be checked at the close-out visits if applicable or state details in the additional national appendix 1.

4. Monitoring of general protocol compliance and data quality

The monitor will verify the compliance to study protocol and study specific procedures.

CRF's will be monitored for completeness and legibility together with a control that corrections are done and properly signed.

A full (100 %) SDV, CRF completeness, and adherence to the study protocol will be checked for the first xx included study subjects at each site and thereafter on xx% of all included study subjects at each site.

As a rule the first included two-three study subjects at each site will be reviewed as described above. An evaluation will be done according to the risk-based assessment and site by site specific adjustments can be done. Describe site-specific monitoring activities in appendix 1.

If any relevant changes of the study staff will take place during an ongoing study a full (100 %) SDV, CRF completeness and adherence to the study protocol will be considered for one or more of the study subjects.

5. Description of monitoring activities related to a risk-based assessment

5.1 Organisation and governance

5.2 Training

5.3 Patients' rights and safety

It will be checked for all trial subjects that informed consent has been correctly obtained by persons delegated for the duty.

It will be checked that all/selected (specify) inclusion- and exclusion criteria for all trial subjects are fulfilled.

5.4 Data

Source data verification will be done for the main endpoint/parameter for all trial subjects.

Describe what to check, and how and when to do it.

5.5 Protocol procedures

It will be checked for all trial subjects that data for main endpoint/parameter have been

collected at the correct time according to study protocol and are evaluated by persons authorized for the task.

5.6 Study drug/IMP

5.7 Safety management

It will be checked that SAE's for all trial subjects are registered and reported correctly according to the study protocol.

5.8 Impact

5.9 Other

6. Monitoring of national and site-specific conditions

See appendix 1 for additional national requirements and site-specific conditions.
No national requirements are relevant.

7. Other monitoring related activities

If any other monitoring related activity will take place it will be described here (e.g. telephone contacts, in-house monitoring activities, monitoring visits at other departments, pharmacy or laboratories).

8. Monitoring of database

If applicable, described the extent of monitoring of database.

9. Commencement

This monitoring plan is valid after sponsor's written signature or written confirmation (i.e. can be confirmed by e- mail or in other written documentation).

10. Evaluation of the monitoring plan

The monitoring plan will be evaluated on ongoing basis, after every approved amendment, and according to sponsor's evaluation after e.g. the second monitoring visit or/once a year/ after an unacceptable degree of deviations.

11. Reports and letters

The monitor will send a written report to sponsor and investigator for information after each monitoring activity. The report is a summary of all relevant findings and emphasises all important actions need to be taken.

The monitor will inform each site about relevant findings and appropriate actions needed to be taken and by whom. **The information can be a copy of the written report, a follow-up letter or oral information.**

12. Signatures

The following monitoring plan is approved by both parties and will apply until up-dates are implemented.

Date

Sponsor

Date

C-GCP unit

Monitoring plan Appendix 1

National requirements and site-specific conditions for xxxxxxxxx write the country

List the additional national requirements for each Nordic country concerning monitoring not included in the monitoring plan signed by the sponsor/national coordinating investigator and the GCP Units concerned (if relevant).

The monitoring is based on SOP for monitoring xxxx developed by (document either in this appendix or in the agreement whether the SOP from the local GCP Units, coordinating investigator or the sponsor should be followed)

Initiation visit

XXX

Monitoring visits

XXX

Close-out visit

XXX

List the site-specific conditions and monitoring activities for each site

Site x

Site x

Signatures

The appendix is approved by all parties.

Date

Sponsor

Date

National coordinating investigator

Date

NC-GCP Unit