1 PURPOSE

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe the requirements for the preparation and completion of the case report form (CRF) and patient reported outcome (PRO) forms for obtaining study-related data in a clinical trial.

This SOP ensures 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 clinical drug trials.

If the sponsor is external, e.g. a pharmaceutical company, the sponsor's SOPs will be used, provided that these are in line with national and international laws, regulations and ICH GCP.

3 RESPONSIBILITIES

3.1 SPONSOR

The sponsor has overall responsibility for ensuring that the CRF and PRO forms are prepared and managed in compliance with this SOP.

The sponsor's responsibilities shall be described in the governing documents (quality system) of the individual health facility / the individual institution. Tasks can be delegated. The delegation of tasks shall be documented.

The national coordinating investigator (for multi-centre studies) or the principal investigator (for single-centre studies) (NCI / PI) have the responsibility for ensuring that assigned tasks are carried out according to the requirements of this SOP.

The sponsor will assign the preparation and management of CRF and PRO forms suitably qualified and experienced individuals.

All staff who carry out these tasks, must possess the necessary qualifications for the task.

If tasks are performed by a third party vendor, in whole or part, this shall be specified in the written agreement between the sponsor and the third party. The agreement will specify activities to ensure that the sponsor's requirements for quality are complied with.

The principal investigator for single-centre studies / national coordinating investigator for multicentre studies will ensure that appropriate CRF and any required PRO forms (paper or electronic) for the collection of study-related data are prepared. They will also ensure that the correct version are available and used by each centre.

The principal investigator for single-centre studies / national coordinating investigator for multicentre trials must ensure that CRF and PRO are or have been tested or validated before use.

The principal investigator for single-centre studies / national coordinating investigator for multicentre studies must approve the CRF and any PRO forms before use and approve any amended versions.

The principal investigator is responsible for the correctly completing all required fields in the CRF. This task may be delegated to other suitably qualified persons. The names and roles of people who have been assigned the task will be entered into the site specific Delegation Log.

3.2 DATA MANAGERS

Data managers will:

- Prepare and test CRFs and PROs
- Review data in trial databases
- Manage auto and manual query process

3.3 MONITORS

Monitors will check the accuracy and completeness of CRF entries, source documents and other trial-related records against each other, including PRO data.

4 PROCEDURES

4.1 GENERAL PRINCIPLES

The CRF and PRO should be designed and completed in order to ensure accurate recording, interpretation, verification and reporting of data from the study, and shall be in accordance with the approved protocol.

Data recorded in the CRF and PRO forms should be de-identified, unless otherwise specifically authorized by the IEC, and a unique identification code (subject number / randomisation number) should be used for each subject.

The subject ID log/participant log should be stored safely with limited access and separate from the electronic trial data. If paper CRF is used, separate archive of CRF and subject ID log/Identification and Enrollment Log should be stored separately if institution procedures requires it. The CRF and PRO must prevent recording of data that could directly or indirectly lead to the identification of the human subject. This is especially important for small populations.

If permitted by local regulations, initials, date of birth and gender will be collected.

To ensure uniformity in the collection of data, it is recommended that CRF completion guidelines are prepared, as necessary. If a new version of the CRF is issued, then the completion guidelines should be revised and if necessary an explanation of what has changed should be included.

Completion instructions for PROs are usually part of the instrument and separate instructions are not required.

A blank original (not completed) CRF and PRO are essential documents, according to ICH GCP and copies must be kept in study file. See SOP Study Files.

There will be additional requirements specific to e-CRF/e-PRO and other electronic systems used in data collection. See SOP Data Management.

4.2 CRF CONSTRUCTION

The data manager may start work on the design of the CRF before the protocol is finalised. The CRF will be finalised when the protocol is final and approved by the relevant authorities.

If the protocol is amended during the study and this has an impact on the data to be collected, the data manager will ensure that the CRF is updated and given a new version number and version date. The new version must be approved by the NCI / PI before it is sent to the various study centres.

The data manager will ensure that CRFs are easy to use, logically constructed and divided into the separate study visits described in the protocol.

The data manager will prepare CRFs which consist mostly of multiple forms for each study visit, continuous forms and final study completion forms. In some studies it is also appropriate to include follow-up visit forms. A study visit is a visit which occurs while the subject is being administered study drug as opposed to follow-up visits, which are intended to evaluate long term safety and / or efficacy of the treatment.

It is usual for adverse events and drug use (concomitant medication) to be collected in modules that are independent of study visits (continuous forms).

When using a paper CRF, the data manager will ensure that all pages are numbered with the page number and the total number of pages. Each page shall be clearly marked with the visit identifier or name (for a continuous form).

4.2.1 CRF outline

The data manager will ensure that all required modules for a study and the study-specific data are included in the CRF. The required modules will usually include, but not be limited to the following:

Selection Criteria:

- Inclusion criteria
- Exclusion criteria
- Date of consent

Study visits:

- Demography (first visit).
- Medical history (first visit)
- Study Procedures (tests / examinations)
- Response to treatment (laboratory results, CT scans etc.)
- Safety variables (laboratory results, etc.)
- Handling and administration of study drug (this can also be a continuous form)
- If necessary, a signature module for the principal investigator or authorised study personnel to confirm that the data is complete and correct

Continuous forms:

- Documentation of adverse events (Adverse Events, Serious Adverse Events)
- Concomitant Medication
- Handling and administration of study drug (depending on the study setup)

Follow-up Visits:

- Study Procedures (tests / examinations)
- Response to treatment (laboratory results, CT etc.)
- Safety variables (adverse events incl. Laboratory results etc.)

End of study form:

- Date and reasons for study termination
- Signature module where principal investigator or sub-investigator confirms that all data are complete and correct

4.2.2 Construction guidelines

The CRF designer should prepare CRFs which are clear, concise and consistent by ensuring that:

- All CRF pages contain fields for recording the study subject's identification code (subject number / randomisation number). It is also recommended to have a field for the centre number
- The data which is to be recorded and measuring scale / unit to be used, must be clearly and unambiguously identified
- Electronic CRFs include logical checks or minimum / maximum values for the data, if possible
- Text fields are used sparingly since textual data is difficult to analyse. If text fields are necessary the designer should ensure that there is enough space

- Features exist to facilitate coding (drug use, diagnoses and / or adverse events)
- Check that the CRF contains exactly the data required by the protocol
- There are fields where one can check if procedures are not carried out and / or are not relevant. If not carried out this should be explained in a separate field
- Familiar terminology is used, including established abbreviations, for the relevant discipline
- There is no duplication of information
- The CRF is dated and version controlled
- The person entering data does not need to perform calculations, unless this is absolutely essential. It is more efficient to perform calculations in the analysis phase of the project.
- Standardised font size, colours, headers, etc. are used throughout the CRF

To ensure accurate recording and interpretation of data, it is recommended that the NCI / PI, a data manager, a statistician and monitor review the CRF prior to its use.

The data manager, the NCI / PI and the statistician if needed should approve the CRF. An email from each person stating that the CRF is approved can be used to document approval.

4.3 TESTING

Data manager must ensure that the CRF and PRO are tested before use. This should be done by entering some representative test data (including errors) to the eCRF / DEA.

Testing / validation should be documented and the documentation should include the test data, and printouts / listings of data and for eCRFs a PDF of the resulting eCRFs.

4.4 UPDATING OF CRFs

If any deficiencies in any parts of a CRF are observed during the study the NCI / PI should ensure that the developers are requested to make the necessary modifications, while at the same time informing all centres about the changes. Every effort should be made to schedule CRF development to avoid the need for design changes once data entry has started.

4.5 DATA MONITORING

Based on a risk evaluation, the monitors may check the accuracy and completeness of CRF entries, source documents and other trial-related records against each other.

Specifically monitors will verify that:

- The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
- Any dose and/or therapy modifications are well documented for each of the trial subjects.
- Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
- Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

Monitors will inform the investigator of any CRF entry error, omission, or illegibility.

Data managers will also review data recorded in the database for missing data, inconsistent data, data outliers. This will be done using automatic and manual queries as defined in the data management plan for the trial.

4.6 USE OF PROS

It is recommended that only validated Quality of Life Forms and other validated instruments or questionnaires forms are used. These often belong to an organisation who owns the copyright and some organisations charge for use of instruments which they own. The NCI / PI must ensure that requirements for licenses and copyrights are satisfied.

If it is necessary to use a PRO other than validated quality life questions the NCI/PI should ensure that the instrument is self-explanatory or if necessary simple instructions should be provided.

4.6.1 Useful links

European Organisation for Research and Treatment of Cancer:
cancer specific quality of life questionnaires and multiple diagnosis specific questionnaire modules for use with different cancer diagnoses.

RAND Medical Outcomes Study Measures of Quality of Life Core Survey from RAND Health
Use of the SF-12 is governed by Quality Metric, which has no affiliation with RAND (payment is required).

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4.7 DATA ENTRY INSTRUCTIONS

Instructions can be included in the eCRF or specified in a separate document.

Data managers and CRF designers should consider including the following in the CRF instructions:

4.7.1 Electronic CRF and paper CRF (All CRF types)

- Never leave any fields blank. If data is unavailable, enter UN (unknown), NK (not known), MD (missing data), ND (not done) or other agreed notation. NA (not applicable) should be used only if the data is not relevant
- Be accurate, data should match the source data. If data is subject to interpretation, obtain expert advice
- Only use standard clinical abbreviations
- Never write the name or social security number of a subject in the CRF

4.7.2 Paper CRF

- Always use a black or blue ball point pen.
- If CRF is made of NCR paper, always use an appropriate separator (cardboard / thick paper)) prior to writing on the CRF
- Use the fields that are provided, do not write in the margins
- Each study visit should be signed and dated by the principal investigator or professionally qualified person who has been delegated the task, to confirm that all the data reported in CRF for a subject is complete and correct

4.7.3 Electronic CRF (eCRF)

- Never share your user ID and password.
- Never store user ID and password in unsecured locations. Try to memorise them so that they do not need to be kept on paper.

4.8 DATA CORRECTION

4.8.1 Electronic CRF and paper CRF (all CRF types)

Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both hand written and electronic changes or corrections.

Procedures for making corrections to CRF data, or for answering queries (including custom correction forms) shall be agreed in advance with the principal investigator for single-centre studies / national coordinating investigator for multicentre studies.

4.8.2 Paper CRFs

Corrections to the sponsor's copy of the CRF (before the original is sent to the sponsor) will be carried out as follows:

- Cross out the incorrect data by drawing one straight line through the incorrect data, so that the original data can still be read
- Write the correct data in close proximity to the original field
- Corrections shall be dated and signed with initials and an explanation of the correction should be provided if it is not obvious why the correction was made
  For example::2009 ~~2010~~ *NBL*

Corrections made to CRF data after the original page has been sent to the data manager will be done using query forms. Query forms are also used to verify data that is outside defined quality standards and specified limits, or where data are unclear or difficult to read.

The data managers will send queries to the principal investigator who will ensure that the query is answered. A copy of the completed and signed query form with be attached to the CRF and the original will be sent to the data manager.

5 DEVIATION MANAGEMENT

Deviation management in a study could be managed according to SOP Protocol Deviation Handling.

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

6 REFERENCES

6.1 EXTERNAL REFERENCES

- ICH Guideline Good Clinical Practice (GCP) E6 (R2), chapter 4 .9, 5.5.
- Good Clinical Data Management Practices Design and Development of Data Collection Instruments.
- Reflection paper, on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. EMA 1. August 2010.

6.2 INTERNAL REFERENCES

- SOP Data Management
- SOP Protocol Deviation Handling

7 ATTACHMENTS

8 DEFINITIONS

- Definisjoner

9 CHANGES SINCE PREVIOUS VERSION

Version 3.1: This SOP replaces SOP 2.7 version 3.0. Monitoring based on a risk evaluation is included under 4.5.