1 PURPOSE

The purpose of this guide is to provide hints and tips for high quality clinical interventional studies in subjects, in addition to the requirements by law. Roles, responsibilities, authorities and distribution of tasks throughout the study will be discussed.

2 SCOPE

Clinical interventional studies are not as heavily regulated as i.e. drug trials or medical device trials.

Examples of clinical interventional studies may be (list is ***not exhaustive***): Radiation therapy studies (including new dosing regiments), diet/exercise interventions, surgical procedures, psychiatric/psychologic interventions, light therapy and medical devices within approved CE-kite marking.

The clinical interventional studies, including pilot studies and experimental treatments, are regulated in the Health Research Act (helseforskningsloven), in the law itself and in the linked regulations. In addition the University hospitals have internal routines for research that also must be followed.

This guideline will bring in elements from ”good clinical practice” (GCP) in clinical intervention studies. GCP is not required by law for the studies in this guideline, but will add quality to the projects, making the most out of resources spent and perhaps making publications accepted quicker.

The guide will be in line with current national regulation. If any suggestion in this guideline contradicts any institutional routine, the institutional routine supersedes this guideline.

The following is not covered in this guide:

- *Drug trials.* These are covered in NorCRIN SOPs “Nasjonale prosedyrer for klinisk utprøving av legemidler (LM SOP-er)”
- *Clinical trials of medical device* when used outside current CE- marking or medical device that do not have CE- marking. This is covered in NorCRIN SOP MU ”Use Of Medical Device In Clinical Trials”
- *Quality assurance of the health service provided.* This may be studies/projects, examinations, evaluations etc. where the intention is to ensure that diagnostics and treatment in fact gives the intended results.
- *Establishing health registers* with research purpose.

3 ROLES, RESPONIBILITIES AND DISTRIBUTION OF TASKS

The institution has the overarching responsibility for organising and the conduct of clinical interventional studies and to ensure they are conducted according to applicable laws and regulations.

The most important functions/roles in clinical interventional studies are; research responsible, project manager and project team member. A short description of the functions, roles, responsibilities and tasks follows in the next chapters.

3.1 RESEARCH RESPONSIBLE

The institution is research responsible for all clinical interventional studies that are organized and done in the institution. This is also the case in multicentre studies where the project manager may belong to a different institution.

The responsibility includes:

- To accommodate for proper organising, start up, conduct, communication, closure and post study management
- Enter into contract with suppliers and cooperating institutions
- Ensure routines for safe data handling and storage of research data
- Where applicable, provide responsible person for research biobank (Health Research Act §26)

3.2 PROJECT MANAGER

The project manager is responsible for

- Developing Research Protocol and subject information sheet/consent form
- Ensuring study subjects are insured, if applicable
- Handling and reporting of study data and developing data capture tool (case report form – CRF) for recording study data
- Archiving and storage of study documentation, study file and institutional electronic document archive (e.g. ePhorte, ESA)
- All communication with Regional Ethics Committee; application form, amendment notifications, ongoing reporting (if applicable) and end of study notification
- Obtaining internal approvals (e.g. information security responsible) and any other external approvals if applicable, according to the routines in the institution
- Ensuring that cooperating institutions are trained on the study and procedures
- Registering the study as applicable (ClinicalTrials.gov and kliniskestudier.helsenorge.no)

In multicentre studies there will be one project manager for all Norwegian cooperating institutions. However, each institution will be research responsible for the research conducted in own institution.

3.3 PROJECT TEAM MEMBERS IN COOPERATING INSTITUTIONS

Cooperating institutions should enter into a written agreement describing each partner's responsibilities and tasks.

There should be a dedicated project team member (Researcher/Investigator) responsible for the conduct of the study in each institution. This person acts on behalf of the project manager, as delegated (defined in the written agreement).

The responsible project team member on each institution should:

- Ensure internal acceptance and approvals for the study
- Facilitate internal agreements with cooperating units/internal partners
- Coordinate and ensure training of other team members in the institution. Written delegation of tasks is recommended (see AI Appendix 02 «Delegation Log»)
- Ensure that the study is conducted according to approved research protocol

- Follow up the study subjects – obtain written informed consent, treat the subjects, handle adverse events/serious adverse events, including reporting any unwanted medical events according to the internal routines at the institution and project plan
- Ensure that ethical, medical, health related, scientific, personal data and information security issues/conditions are handled in the daily running of the study
- Ensure secure data handling and according to research plan/data handling plan if available
- Report study status/progression
- Archive and store documentation (Investigator Site File)

The responsible project team member at the institution may delegate tasks to other named team members if agreed with project manager. Delegation should be in writing. (See appendix 2 «Delegation Log»).

The project manager has the overarching responsibility to ensure that the team members have sufficient competence to conduct the delegated tasks. Only tasks can be delegated, not the responsibility.

4 TASKS IN AN INTERVENTION STUDY

4.1 DEVELOPING RESEARCH PROTOCOL

A detailed Research Protocol must be developed. It has to be version controlled and it should be signed by a representative for research responsible institution and the project manager. A template for Research Protocol can be found in AI Appendix 01.

If the institution has a department for research support this department could possibly be available for advice when it comes to writing project plans. Statistician should be consulted for choosing method and calculating number of participants (power analysis) if this is not within the project manager's expertise.

The NorCRIN SOP LM 1.04 for drug trials may be useful for studies where participants are randomized or studies where treatment is blinded for the subjects/researcher.

4.2 DEVELOPING SUBJECT INFORMATION SHEET AND CONSENT FORM

All study participants must have both written and verbal information about the study and get sufficient time to consider before deciding whether to consent. Written consent must be obtained before any study specific procedures are done. A study specific procedure may be e.g. asking the subject to be fasting at the first visit if this is not standard procedure in usual patient care. It is possible to apply to Regional Ethics Committee for exemption.

The subject information sheet and consent form should be developed based on Regional Ethics Committee's templates and be approved by the Regional Ethics Committee before it is used. The content should be easily understood by the study subjects and as a general rule the participants should sign and date the consent form themselves. The Regional Ethics Committee also has templates for situations where the next of kin will have to consent on behalf of the subject. In the guide to the Health Research Act more information regarding different consent scenarios can be found.

If new information becomes available that may alter the subject's opinion about participating in the study, a new consent for continuing in the study must be obtained, either by signing an updated patient information sheet/consent form or as an amendment to the originally signed document. The amended documents must have approval by the Regional Ethics Committee before they are used. In case of emergency, i.e. new safety

information, subjects should be informed verbally before the written documents are available. All consents (written or verbal) should be documented in the patient's hospital record.

4.3 APPROVALS PRIOR TO STUDY START

4.3.1 Internal approval of the project

Most institutions have a process of obtaining internal approval from the institution, both from department or clinic leader and from the information security officer (this role may be held by the data protection officer in some institutions).

4.3.2 Regional Committee for Medical and Health Research Ethics

All studies under the health research act need to be approved by the Regional Ethics Committee before starting. This implies that documents like Research Protocol and patient information sheet/patient consent form must be part of the application to the Regional Ethics Committee. All written information to be provided to the study participants have to be approved by the Regional Ethics Committee, e.g. questionnaires and adverts/recruitment material.

4.4 CHANGES TO THE RESEARCH PROTOCOL AFTER APPROVAL

If changes to the Research Protocol are required after approval, an updated version (with version number) and amendment form must be sent to Regional Ethics Committee for approval before the changes can be implemented. This is described in the Health Research Act § 11 and on the Regional Ethics Committee homepage.

Changes that are required to ensure the participants safety should be implemented immediately. It is recommended to inform the Regional Ethics Committee by telephone in these cases and to follow up with the written amendment form as soon as possible.

Please Note! If the project is delayed and cannot be completed before the study end date approved by Regional Ethics Committee, an amendment form must be sent to Regional Ethics Committee in due time to get an extension. Data cannot be collected or handled after the approved study end date.

4.5 REGISTER THE STUDY AT CLINICALTRIALS.GOV AND HELSENORGE.NO

All clinical studies testing or comparing different treatments should be registered at ClinicalTrials.gov before starting, also observational studies. Such registration may be a prerequisite for publication of the study results later.

Ministry of Health and Care Services has requested all clinical studies to be registered at the web site kliniskestudier.helsenorge.no. Contact local research support at your institution, or search for procedure in the institution's quality system, if you are not aware of how this is done.

4.6 STUDY MEETINGS

After all approvals are obtained and the study starts, the project manager, or delegate, must ensure that the study staff is trained in all applicable study procedures. This could be done in a study start/kick-off meeting at each site or at a joint meeting for all study sites. Documentation of the training (agenda, minutes, participant lists, agreed delegation lists) should be archived in the study files (general file and site file).

4.7 ACCOUNTABILITY

Depending on the nature of the study, accountability of the intervention in the study or other equipment may be useful. AI Appendix 03 can be adjusted as needed for this use.

4.8 MONITORING

There is no requirement for monitoring of intervention studies that are not drug trials or medical device outside CE-marking. However, independent monitoring of any study may increase the quality. The monitor pays special attention to the participant's rights and safety and the data quality.

4.9 HANDLING AND STORAGE OF RESEARCH DATA

The project manager is responsible for adequate statistical competence, systems and equipment for recording data, data handling and storage of data and samples.

The institution will have routines for storage of research data. Main rule is that all study data must be captured without direct recognisable personal information. All subjects assessed/screened for study participation and who have signed a consent form should be registered and de-identified in a screening log (AI Appendix 04). All subjects included in the study will have a study number that will follow the data (consent form, questionnaires, CRF etc.). A code list (Subject ID Log) connecting the subject number to the subject must be kept with limited access (AI Appendix 05).

Study data for each subject are recorded in a study specific «Case Report Form» (CRF) that reflects the Research Protocol. Data that are not described in the Research Protocol (and hence not approved by Regional Ethics Committee) cannot be collected. The CRF may be electronic (e.g. web based) or on paper.

[Developing and completing Case Report Form (CRF) are further described in NorCRIN SOP LM 2.07 for drug trials with examples.]

Data handling should either be described in the Research Project Plan or in separate "Data Management Plan" (see AI Appendix 06).The database must be "locked" prior to analysing the data (AI Appendix 07).

[Data handling is further described in NorCRIN SOP LM 2.06 for drug trials.]

4.10 SOURCE DOCUMENTS

As a ground rule any data collected in the study must be documented in the subjects' hospital notes or other source document. In this way the data can be reconstructed if needed.

4.11 REPORTING

The project manager and responsible project team member in multi centre studies must follow up internal reporting routines in own institution as applicable. In addition, project manager must report to Regional Ethics Committee, including end of study notification.

In studies with radiation therapy deviations are to be reported internally as described in internal procedures. Accidents and abnormal events are to be reported immediately to the Norwegian Radiation Protection Authority (Statens Strålevern). If there are no acute danger for life, health or environment it can be reported within normal working hours. This can be reported verbally, followed by written report within 3 days.

4.12 STORAGE OF DOCUMENTATION AND ARCHIVING

The project manager is responsible for developing a study specific plan for safe keeping and archiving project documentation. Throughout the study life cycle it is recommended to keep documentation and correspondence on both centre level (Investigator Site File) and study level (Trial Master File). For Table of Content for the study files, see AI Appendices 08 (TOC ISF), 09 (TOC TMF) and 10 (ISF and TMF combined). The study files are to be archived according to the routines in each institution. Patient data (including de-identified data) cannot be stored or archived for a longer period than stated in the Regional Ethics Committee approval and must be destroyed or anonymized (destroying patient ID log) at this date at latest. Ensure that also other documents that has direct person identifying data and subject number (e.g. consent forms) also are destroyed.

4.13 STUDY REPORTS AND PUBLICATIONS

The CONSORT-group has developed a minimum set of recommendations for reporting randomized trials that may be very useful for writing publications for studies comparing two groups. For other study designs, useful information is found here.

5 HANDLING DEVIATIONS

Deviations to the routines at each institution should be followed.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Lov om medisinsk og helsefaglig forskning (Helseforskningsloven) LOV-2008-06-20-44
- Veileder til lov om medisinsk og helsefaglig forskning (helseforskningsloven)
- Lov om helsepersonell m.v. (Helsepersonelloven) LOV-1999-07-02-64 – særlig § 4
- Forskrift om organisering av medisinsk og helsefaglig forskning FOR-2009-07-01-955
- Merknader til Forskrift om strålevern og bruk av stråling FOR 2016-12-16-1659
- ClinicalTrials.gov
- Kliniskestudier.helsenorge.no
- OUS info om registrering i ClinicalTrials.gov og helsenorge.no
- European Medicines Agency – ICH GCP

6.2 INTERNAL REFERENCES

- NorCRIN SOP LM 1.03 Referansedokument
- NorCRIN SOP LM 1.04 Randomisering, blinding og avblinding
- NorCRIN SOP LM 2.06 Data Management
- NorCRIN SOP LM 2.07 Case Report Form (CRF) and Patient Reported Outcome Form Management

7 APPENDICES

- AI Appendix 01 «Research Protocol Clinical study (interventional or observational)»
- AI Appendix 02 «Delegation log»
- AI Appendix 03 «Accountability of Intervention»
- AI Appendix 04 «Screening log»

- AI Appendix 05 «Subject ID log»
- AI Appendix 06 «Data Management Plan»
- AI Appendix 07 «Database lock»
- AI Appendix 08 «Table of Content Investigator Site File, ISF»
- AI Appendix 09 «Table of Content Trial Master File, TMF multicentre»
- AI Appendix 10 «Table of Content ISF-TMF single centre study»

8 VERSION LOG

Version	Changes since previous version	author	Effective date
1.0	N/A	Anne Mathilde Kvamme	July 2017