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1 PURPOSE

The purpose of this guide is to provide hints and tips for high quality clinical interventional and observational (CIO) studies. It will also provide information regarding legal requirements. The guideline will cover roles, responsibilities, authorities and distribution of tasks throughout the study.

2 SCOPE

Clinical interventional and observational studies conducted under the Helseforskningsloven (the health research act) are within the scope of this guideline. Studies where the clinical intervention is additionally regulated, i.e. clinical drug trials and medical device investigations where data is to be used for CE-marking, are not within the scope of this guideline. The latter studies are to be conducted according to the LM SOPs and MU SOP.

Examples of studies covered by this guideline are (the 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- marking.

For different types of interventions additional considerations may be necessary, see enclosures to this guideline.

The clinical intervention studies, including pilot studies, are regulated in Lov om medisinsk og helsefaglig forskning (helseforskningsloven) and in the linked guideline (veileder til lov om medisinsk og helsefaglig forskning). In addition, the hospital's internal research routines must be followed.

This guideline will bring in elements from the Good Clinical Practice guideline (ICH GCP) that are applicable to clinical interventional and observational studies. GCP is not required by law for the studies within the scope of this guideline, but will enhance quality of obtained data, ensure research ethics for study subjects, making the most out of resources spent and will initiate good research structure.

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

The following is **not** covered in this guide:

- *Drug trials.* These are covered in NorCRIN SOPs Clinical trials of medicinal products ("LM SOPs")
- *Clinical trials of medical device* when study results are intended used for CE- marking. This is covered in NorCRIN SOP **MU "**Use Of Medical Device In Clinical Investigations"
- Studies not in scope of the Health Research Act, i.e. not notified to the Regional Ethics Committee (REK) e.g.
    - *Quality assurance studies 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 but where the collection of data does not imply direct contact with the subject.
    - *Establishing health registers* with research purpose.

3 ROLES, RESPONSIBILITIES AND DISTRIBUTION OF TASKS

3.1 Research responsible institution

The institution where the project manager is employed is the responsible coordinating research institution for the study. This institution is also the data controller according to General Data Protection Regulation (GDPR), either alone or as a joint controller together with the cooperating institutions.

3.2 Project manager

The project manager (in person) is responsible for the day-to-day conduct of the research project, and should have the necessary research qualifications and experience to be able to fulfil the obligations.

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 its 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).

3.4 Roles and Responsibility overview

Tasks	Research Responsible Institution	Project Manager	Responsible in cooperating institutions
R = Responsible D = Delegated task			
Planning phase			
Ensure internal approval of the study		R	R
Obtain relevant advise regarding personal data protection and information security (storage and transfer of data etc.) to ensure that a Data Protection Impact Assessment (DPIA) is conducted if required and that legal basis for handling personal data and health data is present according to institutional routine		R	R
Ensure proper handling of human biologic material according to institutional routine and assign responsible person for research biobank	R	D	D
Ensure that the institution where the responsible researcher is employed has systems and routines that safeguards that research data is handled and stored properly according to institutional routine	R		R
Obtain approval of the investigation and any substantial changes from REK prior to start. Ensure all participating centers are recorded as research responsible institutions.		R	
Register the study at clinicaltrials.gov and at the institution's clinical study directory (web site)	R	D	
Develop study protocol, information sheet, consent form,), Case Report Form (CRF) / questionnaires and study specific guidelines (incl data management plan).	R	D	
Ensure supplies, if applicable		R	
If applicable, ensure that the investigation is monitored		R	D
Enter into written agreements with cooperating institutions and others	R	D	

Tasks	Research Responsible Institution	Project Manager	Responsible in cooperating institutions
Make agreements with internal cooperating departments		D	R
Establish Trial Master File (TMF) for the trial and Investigator's Site File (ISF) at each investigational center	R	D	
Conduct phase			
Ensure that the investigation is conducted according to approved study protocol		R	D
Obtain approval of substantial amendments from REK		R	
Update clinicaltrials.gov and the institution's clinical study directory when inclusion of study subjects is stopped.	R	D	
Ensure sufficient supplies throughout the study		R	
Develop written overview of tasks delegated to study staff			R
Follow the Data Management Plan		R	
If applicable, ensure monitoring of the investigation is conducted and followed up		R	R
Supervise study staff conducting delegated tasks or function and ensure they are qualified and are properly trained		R	D
Conduct necessary training of all new study staff in the protocol and study specific guidelines		R	D
Keep Trial Master File TMF updated with relevant information		R	
Keep Investigator Site File ISF updated with relevant information			R
Report deviations according institution's internal procedures		R	R
Close-out phase			
Close and archive the clinical investigation	R	R	R
Submit end of study notification to REK		R	
Ensure that electronic systems used for archiving is according to institutional routines	R	D	R
Ensure ones institution is aware of the storage location	R		R

Tasks can be delegated. 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 INTERVENTIONAL 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 the research responsible institution and by the project manager. The protocol template from the Transcelerate website is recommended to use, and access guidance document is available.

Examples of Research Protocols are available at NorCRINs website.

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

For studies where participants are randomized to intervention or studies where treatment is blinded for the subjects/researcher, see SOP Randomisation, Blinding and Unblinding.

4.1.1 Patient Reported Outcome (PRO)

Many research protocols contain patient questionnaires and other data reported directly from the study participants. In enclosure 9.1 the use of PROs is further expanded.

4.2 Subject information sheet and consent form

Before consenting to a study all study subjects must be informed both verbally and in writing and must be given ample time before deciding. Written consent must be obtained before any study specific procedures are performed. 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 REK for exemption.

The subject information sheet and consent form should be created based on REK's templates and must receive REK's approval 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. REK also has templates for situations where the next of kin will have to consent on behalf of the subject. In veileder til medisisnk og helsefaglig forskning 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 REK 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 medical records.

4.3 Approvals prior to study start

4.3.1 Internal approval of the study

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 (REK)

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 REK. All written information to be provided to the study participants have to be approved by the REK, 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 REK for approval before the changes can be implemented. This is described in the Health Research Act § 11 and on the REK's homepage.

Changes that are required to ensure the participants safety should be implemented immediately. It is recommended to inform the REK 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 REK, an amendment form must be sent to REK in due time to get an extension. Data cannot be collected, analysed or otherwise processed 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, including observational studies. Such registration may be a prerequisite for publication of the study results later. This process may take weeks to complete, ensure complete before recruitment starts. Please follow your institution's procedures for registering a study at clinicaltrials.gov.

Ministry of Health and Care Services has requested all clinical studies to be registered at the web site kliniskestudier.helsenorge.no. The clinical studies are first registered at the hospital web-site and transferred from there to the helsenorge platform. Contact local research support at your institution, or search for procedure in the institution's quality system, for instructions.

4.6 Study start

After all approvals are obtained and agreements signed (cooperating units/institutions), the study start can be planned. The project manager 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 (TMF and ISF).

4.7 Accountability

Depending on the nature of the study, accountability of the intervention in the study or other equipment may be useful. Appendix 3 can be adjusted as needed for this use.

4.8 Monitoring

Monitoring is an independent quality control performed to ensure that the study complies with the protocol and regulations. The monitor pays special attention to the participant's rights and safety, and the quality of the data. There is no requirement for monitoring of studies covered by this guideline. However, independent risk-based monitoring of any study may increase its quality. The extent of monitoring in a study with a risk based monitoring approach would depend on several factors, e.g. complexity of the study, patient numbers involved, staff experience etc. Specific monitoring report templates are developed to accommodate interventional studies, appendix 11-13.

4.9 Handling, storage and transmission of research data and samples

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. The main rule is that all study data must be captured without direct recognisable personal information. All subjects screened for study participation and who have signed a consent form should be registered and pseudonymised in a screening log (appendix 4). All subjects included in the study will have a study number that will follow the data (consent form, questionnaires, CRF etc.). A code list connecting the subject number to the subject must be kept with limited access (appendix 5).

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 REK) cannot be collected. The CRF may be electronic (e.g. web based) or on paper. Participating institutions must follow internal procedures for obtaining any applicable approvals for safe transfer of data from local institution to external database.

Developing and completing CRF are further described in Case Report Form (CRF) and patient reported outcome.

Data handling should either be described in the Research Protocol or in separate "Data Management Plan" The database must be "locked" prior to analysing the data, to ensure that data are not changed after the analysis has started. NorCRIN LM SOP for Data Management describes this in detail.

Data handling is further described in Data Management.

4.10 Source documents

As a ground rule any data collected in the study should origin from a source document. The source document is the first entry point of data. This could be e.g. the subjects medical records, a laboratory report, a subject questionnaire. Some data may be recorded on work sheets before entered into the eCRF, in these cases the work sheets are source data. In this way the data can be reconstructed if needed and is especially important for the main study endpoints.

4.11 Reporting

The project manager and responsible project team member in multicentre studies must follow internal reporting routines as applicable. In addition, project manager must submit anend of study notification to REK. Additional or extraordinary reports will only be required in cases where REK deems this necessary.

In trials involving radiation therapy, accidents and abnormal events related to the radiation treatment 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 of 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 Appendix 8-10. 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 REK approval and must be destroyed or anonymized (destroying subject ID log) at this date. Ensure that also other documents that have direct person identifying data and subject number (e.g. consent forms) 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. NorCRIN SOPs for Protocol deviation handling can be used for studies under this guideline, adjust as applicable

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
- Lov om organisering av forskningsetisk arbeid (forskningsetikkloven) LOV-2017-04-28-23
- 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
- Lov om biobanker (biobankloven) LOV-2003-02-21-12
- Merknader til Forskrift om strålevern og bruk av stråling FOR 2016-12-16-1659
- ICH GCP R2

6.2 Internal references

- NorCRINs referansedokument
- NorCRIN SOP LM 2.04 Protocol Deviation Handling
- NorCRIN SOP LM 2.05 Randomisering, blinding og avblinding
- NorCRIN SOP LM 2.10 Data Management
- NorCRIN SOP LM 2.11 Case Report Form (CRF) and Patient Reported Outcome (PRO) Form Management

7 APPENDICES

- Appendix 2 «Delegation log»
- Appendix 3 «Accountability of Intervention»
- Appendix 4 «Screening log»
- Appendix 5 «Subject ID log»
- Appendix 8 «Table of Content Investigator Site File, ISF»
- Appendix 9 «Table of Content Trial Master File, TMF multicentre»
- Appendix 10 «Table of Content ISF-TMF single centre study»
- Appendix 11 «Initiation Report CIO»
- Appendix 12 «Monitoring Report CIO»
- Appendix 13 «Close-Out Report CIO»

8 VERSION LOG

Version	Changes since previous version	author	Effective date
1.0	N/A	Anne Mathilde Kvamme	
2.0	General Review Observational studies included Monitoring visit reports included Enclosures with study type specific guides included	Anne Mathilde Kvamme	March 2021

9 ENCLOSURES

9.1 Patient reported outcomes

Inclusion of patient-reported outcomes in a clinical study

Patient Reported Outcomes (PRO) are reports coming directly from patients, about how they function or feel in relation to a health condition and its therapy (1). PRO measures (PROM), questionnaires or interviews, capture issues important to patients, such as health-related quality of life (HRQoL), symptoms and coping. The use of PROM is particularly relevant to support treatment decisions in trials demonstrating a small or no difference in survival, in studies with elderly and patients with chronic diseases that emphasize maintenance of quality of life and good function.

Available guidelines, The SPIRIT-PRO Extension (2) should be used to describe PROM in the study protocol. In order to report patient-reported outcomes (PRO) in randomized studies we recommend consulting the CONSORT-PRO extension (3).

Important PRO items to be included in the study protocol:

Describe rationale for PROM and the selected questionnaire's ability to answer the research question.

Describe the validity of the instrument for the patient group in question and for the relevant language.

State specific PRO objectives (primary or secondary) or hypotheses and describe specific PRO endpoint (concept/ domain) of interest.

Include a schedule for PRO assessments. Choose reasonable time points to meet the endpoint.

Describe management strategies for minimizing avoidable missing data in data management and statistical methods for handling missing data (eg. approach to imputation or sensitivity analyses).

1 Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health. 2007;10 Suppl 2:S125-37.
2 Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA. 2018;319(5):483-94.
3 Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA. 2013;309(8):814-22.

9.2 Specifics for radiation therapy

Radiation therapy is regulated through «Strålevernforskriften» -Regulations on Radiation Protection and Use of Radiation[1]. By regulation the professions included in radiotherapy are oncologist, radiotherapy technician and medical physicist.

Important topics that should be described in intervention study protocols with radiotherapy:

- Dose prescription: dose fractionation schedule, including total treatment time (in days) and principle for normalization
- Patient positioning and immobilization
- Imaging for treatment planning
- Definition of target volumes, critical structures and margins, including contouring guidelines (or reference to such guidelines) 2,3,4
- Compliance criteria: dose volume constraints (soft and hard) for target volumes and organs at risk, including treatment planning priorities
- Treatment verification and reporting

1. https://www.dsa.no/regelverk
2. International Commission on Radiation Units and Measurements, ICRU. Prescribing, recording and reporting photon beam therapy. ICRU report 50. Bethesda, ML: ICRU, 1993.
3. International Commission on Radiation Units and Measurements, ICRU. Prescribing, recording and reporting photon beam therapy (Supplement to ICRU report 50). ICRU report 62. Bethesda, ML: ICRU, 1999.
4. International Commission of Radiation Units and Measurements, ICRU. Prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU report 83. Bethesda, ML: ICRU, 2010.

9.3 Specifics for exercise studies

9.3.1 Study conduct

There is no additional special regulation for these studies. However, the LM SOPs may be used regardless to ensure the best study quality. The drop-out rate should be carefully considered, as a 20% drop-out is normal in exercise-training interventions.

9.3.2 Safety

The health status of the participants needs to be evaluated. There are several precautions regarding exercise training in different diseases. The type of exercise is to be evaluated in the same context.

9.3.3 Risk mitigation

Pre-exercise testing depending on disease is recommended to ensure the safety of the participants. In some circumstance the intervention needs to be performed at a place where medical assistance is easily available, e.g. in hospital training facilities. Equipment for resuscitation should be available.

Recommended reading:

ACSM's Guidelines for Exercise Testing and Prescription, 10th Edition

It is recommended to follow the LM SOPS and disregard the requirements regarding Regulatory Approval, and Safety reporting. Study Monitoring is recommended although not required.

How to Construct, Conduct and Analyze an Exercise Training Study? Front Physiol (2018)

Caution this drug may cause serious harm! Why we must report adverse effects of physical activity promotion, Br J Sports Med (2015)

9.4 Specifics for diet supplements

9.4.1 Classification: Drug or Diet Supplement?

Clarify whether diet supplement is classified as drug or not. Regulated by "forskrift om kosttilskudd". There is a grey zone between plant based drugs and diet supplements as herbs may be both food and medicine.

The Norwegian Medicines Agency will advise whether the product in question is to be considered drug or supplements.

Contact NoMA at: klassifisering@legemiddelverket.no

9.4.2 Import of Diet Supplement from 3. Country

The Norwegian Food Safety Authority ("Mattilsynet") are managing the regulations for Diet Supplements. If the supplement in question is not marketed in Norway / EU / EEC import needs to be reported to The Norwegian Food Safety Authority. Every shipment must be registered at least 24 hours before arrival. The Norwegian Food Safety Authority may inspect the shipment at arrival. If not registered 24 hours prior to arrival the shipment must be quaranteened and not opened until 24 hours after registration (weekend excluded).

Only personnel with "Altinn" access for the institution can register import / shipment. Clarify who this is in your institution.

Registration is done via "Mattilsynets skjematjenester"

9.4.3 Study conduct

There is no additional special regulation for these studies. However, the LM SOPs may be used regardless to ensure the best study quality. If used, requirements relating to regulatory approval and safety reporting can be disregarded. Study monitoring is highly recommended although not required

9.5 Specifics for medical device studies within approved CE-marking

There is no special regulation for these studies. However, the MU SOP may be used regardless to ensure the best study quality. If used, requirements relating to regulatory approval and safety reporting can be disregarded. Study monitoring is highly recommended although not required