

STANDARD OPERATING PROCEDURE (SOP)
USE OF MEDICAL DEVICE IN CLINICAL TRIALS

Clinical trials of medical device(s) is regulated in [Norsk Standard NS-EN ISO 14155:2011](#)
Clinical investigation of medical devices for human subjects. Good Clinical Practice.

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1 PURPOSE

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe the overarching roles, responsibilities, authority and distribution of tasks when planning, initiating, conducting and completing clinical trials with a medical device.

“Medical device” means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process, or
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means.

This SOP will ensure that applicable laws and regulations are followed.

The way to CE marking and placing on the market of a medical device is thoroughly described on the [web page](#) of the Norwegian Medicines Agency. If the sponsor's institution has a section for innovation, or has established a cooperation with a Technology Transfer Organisation (e.g. [Inven2](#), [BTO](#), [NTNU TTO](#)), it can be useful to cooperate with them in this matter.

2 SCOPE

This SOP is applicable for clinical trials of medical devices that are not CE marked or studied outside approved CE marking.

For studies where a drug is investigated as well as the medical device, the SOPs for drug trials ([LM SOPs](#)) apply as well.

The following applies to this procedure:

- Medical and health professional research with a medical device, according to the [Health Research Act](#), including experimental treatment and pilot studies.
- All equipment produced and used for *in vitro* diagnosis is regarded as a medical device.
- The intended use of a mobile app determines whether it meets the definition of a «device». When the intended use of a mobile app is for the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or any function of the body of man, the mobile app is a device. It is wise to involve information security officer of the institution early when developing such «health apps».

The following are not in the scope of this procedure:

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- Quality control of the health service, defined as studies/projects, examinations, evaluations etc. done with the purpose of controlling that diagnosing and treatment in fact give the expected results.
- Clinical trials with medical device used solely within valid CE marking.

If the sponsor is external, e.g. a commercial company, the sponsor's SOPs may be used as long as they are in line with Norwegian and European laws and regulations.

3 ROLES, RESPONSIBILITIES AND DISTRIBUTION OF TASKS

The most important roles in clinical trials of medical devices are; sponsor, cooperating institutions, Project Manager (National Coordinating Investigator / Principal Investigator in single centre trials), Principal Investigator, study site staff and monitor. A short description of their roles, responsibilities and tasks are given below.

3.1 SPONSOR

In an *investigator initiated study* the sponsor of the study is usually the institution where the Principal Investigator (single centre study) or the National Coordinating Investigator (multicentre study) has their main employment.

In contracted research for industry or other organisations in Norway or abroad, industry / external partner will usually be the sponsor.

The sponsor holds legal responsibility for the study. In the institution the legally responsible person is the supreme leader. In hospitals, for example, this responsibility is often delegated to department or clinic level ensuring that the responsibility is not too distant to the operative part.

Even though the institution is sponsor for investigator initiated trials, the funding for the trials may come from external sources as well as from internal.

Many sponsor tasks may be delegated to the National Coordinating Investigator / Principal Investigator of the study.

Sponsor's tasks include:

- Facilitate the organisation, start up, conduct, closure, reporting and implementing health research projects (cannot be delegated)
- Ensure routines for safe treatment and secure storage of research data

The following sponsor tasks may be delegated to the National Coordinating Investigator / Principal Investigator:

- Develop written contracts with suppliers and cooperating institutions
- Develop Clinical Investigational Plan and subject information sheet / consent form in cooperation with the Principal Investigator
- Contact the producer of the medical device to be tested (or it's representative) e.g. for supportive documentation
- Develop Investigator's Brochure

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- Ensure study participants are insured
- Write application, amendments, report adverse events and write study report to the regulatory authorities (i.e. Norwegian [Medicines Agency](#))
- Appoint responsible person for research biobank in according to the [Health Research Act § 26](#), if applicable
- Obtain external approvals from regulatory authorities (i.e. the Norwegian [Medicines Agency](#)) and register the trial ([ClinicalTrials.gov](#) and [kliniskestudier.helsenorge.no](#) (in Norway))
- Conduct start-up meeting(s)
- Provide medical device for the study
- Ensure monitoring of the study
- Receive serious adverse events (SAE) reports from Principal Investigator(s)
- Process and report study data including development of Case Report Form (CRF) for capturing study data
- Archive and store study documentation (Trial Master File - TMF)

3.2 COOPERATING INSTITUTIONS

According to regulations regarding organising of medical and health related research, more than one institution may be regarded as research responsible institution. Cooperating institutions will be responsible for the research in the study conducted at their own institution.

3.3 NATIONAL COORDINATING INVESTIGATOR

In multicentre studies there will be a National Coordinating Investigator that will be Project Manager for the Norwegian part of the study. The National Coordinating Investigator is usually the Principal Investigator at one of the study sites. However, this is not a requirement.

The National Coordinating Investigator is responsible for all communication with the Regional Ethics Committee (REC); application, amendments, reporting during the study (if applicable) and end of study notification.

3.4 PRINCIPAL INVESTIGATOR

The Principal Investigator is responsible for the trial at a specific site, hospital or other institution. According to the Health Research Act the Principal Investigators must have documented sufficient competency in their CVs to lead and conduct the trial in their own institution.

In single centre trials the Principal Investigator will have the responsibilities held by the National Coordinating Investigator in multicentre trials in addition to the responsibilities and tasks listed below.

Responsibilities and tasks includes to:

- Ensure internal acceptance and approval in own institution
- Obtain agreements with cooperating units / partners
- Ensure training of study staff and document in writing the delegation of tasks (see [MU Appendix 03 «Delegation Log»](#))
- Follow-up the trial participants – collect written consent, register, treat, handle [AE/SAE](#) etc.

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- Ensure that the trial is conducted in accordance with the approved Clinical Investigational Plan (CIP)
- Ensure that ethical, medicinal, health related, scientific, personal data protection and information security are aspects that are covered in the daily routines at the trial site
- Ensure safe handling of research data
- Ensure safe storage, handling and accountability of medical device (see [MU Appendix 4 «Accountability of Medical Device»](#))
- Report study status, progression and any [serious adverse events](#) to sponsor and internally according to the institution's routines
- Archive and keep documentation (Investigator Site File – ISF and Institutional electronic document archive (e.g. ePhorte, ESA) as applicable)
- Report deviations according to internal procedures at own institution

3.5 STUDY STAFF

The Principal Investigator may delegate tasks to named study staff in the same institution contributing to the study and/or cooperating partners. The delegation needs to be in writing and documented in a delegation log (see [MU Appendix 03 «Delegation Log»](#)).

The Principal Investigator has the responsibility to ensure that the study staff members have sufficient competence to conduct their delegated tasks. Only defined tasks can be delegated, not the responsibility.

However, study staff members that are defined as health personnel according to the [Health Personnel Act](#) (§48), are independently responsible for sound patient treatment (§ 4).

3.6 MONITOR

Clinical trials of medical device must have a person (monitor) responsible for [monitoring the trial](#) (see [ICH GCP 5.18](#)). The monitor receives their assignment from the sponsor. The monitor can be internal or external, but cannot be any of the trial staff working on the trial in question.

4 DETAILED DESCRIPTION OF TASKS

4.1 APPROVALS PRIOR TO TRIAL START

4.1.1 Department/clinic head and data protection / information security officer

Most institutions have a process of obtaining internal approval from the institution, both from department or clinic head and information security officer.

4.1.2 Regional Committee for Medical and Health Research Ethics (REC)

All trials under the Health Research Act need to be approved by [REC](#) before starting. This implies that documents like Clinical Investigational Plan and patient information sheet / patient consent form must be part of the REC application. All written information to be provided to the trial participants has to be approved by REC, i.e. questionnaires and adverts/recruitment material.

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4.1.3 The Norwegian Medicines Agency and the Norwegian Directorate for Civil Protection and Emergency Planning

Clinical trials of medical devices outside approved CE marking will also need [approval from the Norwegian Medicines Agency](#) (with link to the notification form), see Guidance on the Notification Form for Clinical Investigation of Medical Devices in Norway. Clinical trials of medical device must be reported to the Norwegian Medicines Agency at least 60 days prior to the planned trial initiation and the trial cannot be started until the trial is approved.

If the trial involves electro-medical device additional approval from the Directorate for Civil Protection and Emergency Planning is required. The Norwegian Medicines Agency will forward the application to the Norwegian Directorate for Civil Protection.

The Norwegian Medicines Agency has a dedicated e-mail address for medical device:
medisinsk.utstyr@legemiddelverket.no

4.2 REGISTER THE TRIAL AT CLINICALTRIALS.GOV AND AT HELSENGORGE.NO

All clinical trials 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 trials to be registered at the web site kliniskestudier.helsenorge.no. Contact local research support at your institution if you are not aware of how this is done.

4.3 DEVELOPING CLINICAL INVESTIGATIONAL PLAN

A detailed project plan (Clinical Investigational Plan (CIP)) must be developed. It has to be version controlled and it must be signed by sponsor and Principal Investigator (National Coordinating Investigator in multicentre studies). A template for The Clinical Investigational Plan can be found in [MU Appendix 01](#).

4.4 CHANGES TO THE CLINICAL INVESTIGATIONAL PLAN AFTER APPROVAL

If changes to the Clinical Investigational Plan 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](#) (see your regional REC) 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 REC, an amendment form must be sent to REC in due time to get an extension. Data cannot be collected or handled after the approved study end date.

All substantial amendments to the Clinical Investigational Plan should also be approved by the [Norwegian Medicines Agency](#) and response must be received before implementing the change.

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4.5 DEVELOPING SUBJECT INFORMATION SHEET AND CONSENT FORM

All trial participants must receive both written and verbal information about the trial and get sufficient time to consider before deciding whether to consent. Written consent must be obtained before any trial specific procedures are done. A trial 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 REC for exemption.

The subject information sheet and consent form should be developed based on REC's templates and be approved by REC before it is used. The content should be easily understood by the trial subjects and as a general rule the participants should sign and date the consent form themselves. REC also has templates for situations where the next of kin will have to consent on behalf of the subject.

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 REC approval before they are used. In case of emergency, e.g. 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.

A subject information sheet / consent form template customised for medical device, based on REC's template, is in [MU Appendix 02](#).

4.6 INSURANCE

The application to the Norwegian Medicines Agency must be accompanied by an [insurance](#) statement for the participants, either through a private insurance company or [The Norwegian System of Patient Injury Compensation](#) (NPE). Usually the trial subjects are covered through NPE, but a confirmation is required.

If a trial subject experience an injury or complication as a result from participating in the trial, the subject should immediately be informed about the injury, his/her rights and the option of seeking compensation.

4.7 TRIAL MEETINGS

After all approvals are obtained and the trial starts, the National Coordinating Investigator / Principal Investigator must ensure that the trial staff is trained in all applicable study procedures in a trial initiation visit at each site or at a joint investigator's meeting. The meeting documentation; e.g. agenda, minutes/report, participants, agreed delegation of tasks should be archived in Trial Master File (TMF) (see [MU Appendix 12/13](#) for multi- or single centre studies) and in the Investigator Site File (ISF) (see [MU Appendix 11/13](#)), see 4.13 in this SOP.

It is recommended to have regular trial meetings with minutes to be archived in TMF, copy to ISF.

4.8 STORAGE AND ACCOUNTABILITY OF TRIAL MEDICAL DEVICE

The medical device on trial should always be stored in accordance with the manufacturer's specification and out of reach of unauthorized personnel.

One should know, at any time during the trial, where the medical device under study is located; both used and unused devices. There is a form available for capturing this, [MU Appendix 04](#).

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4.9 MONITORING

Sponsor will provide a monitor to oversee the conduct and progress of the trial, with special attention to the participant's rights, safety, data quality and documentation according to the regulation. A monitoring plan should be available at the start of the trial. The monitor will conduct regular visits and report to the sponsor in a customised monitoring report.

[Monitoring is further described in [NorCRIN SOP LM 1.05](#) for drug trials (Norwegian). Templates for monitoring of drug trials are available in appendices [02](#), [04](#), [06](#) and [08](#) to NorCRIN SOP LM 1.05, and can be adjusted for trial with medical device.]

4.10 HANDLING AND STORAGE OF RESEARCH DATA

All trial data must be captured without direct recognisable personal information. All subjects assessed/screened for trial participation and who have signed a consent form should be registered and de-identified in a screening log ([MU Appendix 05 «Screening Log»](#)). All subjects included in the trial 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 identification must be kept with limited access ([MU Appendix 06 «Subject ID Log»](#)).

Trial data for each subject are recorded in a trial specific «Case Report Form» (CRF) that reflects the Clinical Investigational Plan. Data that are not described in the Clinical Investigational Plan (and hence not approved by authorities) cannot be collected. The CRF may be electronic (i.e. web based) or on paper.

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

Sponsor must ensure access to proper statistic competence and systems for registering data, data handling and storage of data and samples. The institution will have procedures for safe storage of data for research.

Data handling should either be described in the Clinical Investigational Plan or in separate «Data Management Plan» (see [MU Appendix 07](#)). Any changes to the Data Management Plan after approval will be reflected in the Data Management Report (DMR). The Data Management Report template should be used when writing the DMR ([MU Appendix 08](#)).

The database must be «locked» prior to analysing the data ([MU Appendix 09](#)).

[Data management is further described in [NorCRIN SOP LM 2.06](#) for drug trials.]

4.11 REQUIREMENT FOR SOURCE DOCUMENTS

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

4.12 REPORTING

Each Principal Investigator must follow the internal reporting procedures in their own institution. In addition, the National Coordinating Investigator is responsible for reporting to REC and other external authorities.

End of study notification must be sent to REC. Study Report must be sent to the Norwegian Medicines Agency.

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All Serious Adverse Events and equipment failure must be reported to sponsor immediately, but no later than 3 calendar days after awareness of the event. Sponsor must then [report to the Norwegian Medicines Agency](#) immediately but no later than 2 calendar days after awareness of the event. Definitions are given in the Clinical Investigational Plan template; reporting form is in [MU Appendix 10](#).

If there are deaths where electro medical equipment is involved, this must be reported to DSB ([Norwegian Directorate for Civil Protection and Emergency Planning](#)) on phone +47 33 41 25 00 no later than the following working day.

4.13 STORAGE OF DOCUMENTATION AND ARCHIVING

Throughout the trial all required documentation and correspondence are kept in Investigator Site File (ISF) / local trial archive and in Trial Master File (TMF) /sponsor's study archive. The ISF should be available for all trial staff. MU Appendices 11-13 are [table of contents for Investigator Site File](#), [Trial Master File](#), and [a combined version \(ISF and TMF\) for single centre studies](#).

When the trial is completed (all subjects have completed last visit) and the trial report/publication is available, the trial documentation should be archived (TMF, ISF, CRFs). The documents should be kept for 15 years for trials involving medical device that is an implant and 10 years for medical device that are not an implant.

4.14 TRIAL REPORT, PUBLICATIONS

The CONSORT-group has developed a [minimum set of recommendations for reporting randomized trials](#) that may be very useful for writing publications for trials comparing two groups. For other trial design useful information is found [here](#).

For medical devices there is also a requirement to the content of the trial report (Clinical Investigation Report), see [MU Appendix 14](#).

5 HANDLING DEVIATIONS

Deviations to this SOP should be handled according to each institutions procedures.

5.1 EXTERNAL REFERENCES

- [Norsk Standard NS-EN ISO 14155:2011](#)
- [Council Directive 93/42/EEC of 14 June 1993 concerning medical devices](#)
- [Health Research Act](#) (English): [Lov om medisinsk og helsefaglig forskning](#) (Helseforskningsloven) LOV-2008-06-20-44 – especially §§ [5-6](#) (Norwegian)
- [Health Personnel Act](#) (English): [Lov om helsepersonell m.v.](#) (Helsepersonelloven) LOV-1999-07-02-64 – especially § [4](#) (Norwegian)
- Act and Regulations on medical device: [Lov om medisinsk utstyr](#) LOV-1995-01-12-6 (Norwegian) and [Forskrift om medisinsk utstyr](#) FOR-2005-12-15-1690 (Norwegian)
- Regulations concerning organising of medical and health related research: [Forskrift om organisering av medisinsk og helsefaglig forskning](#) FOR-2009-07-01-955 (Norwegian)
- Norwegian Medicines Agency – [Clinical investigation of medical devices](#) (English) – [Klinisk utprøving og evaluering av medisinsk utstyr](#) and [Medisinsk utstyr](#) (Norwegian)

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- [Glossary Medical Device](#)
- [The Norwegian System of Patient Injury Compensation](#) (English) – [NPE](#) (Norwegian)
- [ClinicalTrials.gov](#)
- [Oslo University Hospital \(OUS\) info](#) regarding registration on ClinicalTrials.gov and helsenor.no (Norwegian)
- [MEDDEV 2.7/3 Clinical investigations: serious adverse event reporting](#)
- [European Medicines Agency – ICH GCP](#)
- [Melding om feil og uønskede hendelser med elektromedisinsk utstyr](#) (Norwegian)

5.2 INTERNAL REFERENCES

- [NorCRIN SOP LM 1.03](#) «Referansedokument» (Norwegian)
- [NorCRIN SOP LM 1.04](#) «Randomisering, blinding og avblinding» (Norwegian)
- [NorCRIN SOP LM 1.05](#) «Monitorering» (Norwegian)
- [Appendix 02](#) to NorCRIN SOP LM 1.05 «Study initiating monitoring report»
- [Appendix 04](#) to NorCRIN SOP LM 1.05 «Monitoring report»
- [Appendix 06](#) to NorCRIN SOP LM 1.05 «Final trial close-out monitoring report»
- [Appendix 08](#) to NorCRIN SOP LM 1.05 «Monitoring Log»
- [NorCRIN SOP LM 2.06](#) «Data Management»
- [NorCRIN SOP LM 2.07](#) «Case Report Form (CRF) And Patient Reported Outcome (PRO) Form Management»

6 APPENDICES

- [MU Appendix 01 «Clinical Investigational Plan \(CIP\)»](#)
- [MU Appendix 02 «Information sheet and consent for medical device. Norwegian template»](#)
- [MU Appendix 03 «Delegation Log»](#)
- [MU Appendix 04 «Accountability of Medical Device»](#)
- [MU Appendix 05 «Screening Log»](#)
- [MU Appendix 06 «Subject ID Log»](#)
- [MU Appendix 07 «Data Management Plan»](#)
- [MU Appendix 08 «Data Management Report»](#)
- [MU Appendix 09 «Database Lock»](#)
- [MU Appendix 10 «SAE reporting form»](#)
- [MU Appendix 11 «Table Of Content ISF»](#)
- [MU Appendix 12 «Table Of Content TMF multicentre»](#)
- [MU Appendix 13 «Table Of Content ISF-TMF combined single-centre study»](#)
- [MU Appendix 14 «Trial report»](#)

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7 VERSION-LOG

Version	Changes since previous version	Author	Effective date
1.0	N/A	Anne Mathilde Kvamme	July 2017
2.0	Regulatory Authority for clinical medical device trials changed from the Directorate of Health to The Norwegian Medicines Agency Update of MEDDEV 2.7/3 reference	Anne Mathilde Kvamme	Jan 2018