STANDARD OPERATING PROCEDURE (SOP)

Clinical Investigations with medical device

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1 PURPOSE

The purpose of this Standard Operating Procedure - SOP is to describe the overarching roles, responsibilities, authority, and distribution of tasks when planning, initiating, conducting, and completing clinical investigation on medical devices. Specifically, for investigations where approval from regional ethics committee (REC) and National Competent Authority (as applicable) is required to commence, as well as to ensure that applicable laws and regulations are followed.

2 SCOPE

This SOP is valid for all clinical investigations on medical device sponsored by hospitals that have implemented the NorCRIN SOPs.

This procedure is only applicable where the institution is initiating a clinical investigation and taking the role as sponsor.

The requirements are applicable for clinical investigations for both non-CE marked devices intended for commercialization and CE marked devices to be investigated outside the scope of intended use. Please note that mobile apps may meet the definition for medical device. Additionally, the procedure is applicable for concept studies/feasibility studies and use that was formerly covered through in-house procedure. It will also apply to certain post marketing clinical follow-up (PMCF) studies, e.g. when subjects are submitted to additional procedures that are invasive or burdensome. For more information regarding the latter, see Medical Device Regulation (MDR) Article 74.
For studies where a drug is investigated in combination with the medical device, the SOPs for drug trials might apply as well.

In Vitro Diagnostic performance evaluation is **not** in scope of this procedure.

3 TERMS AND ABBREVIATIONS

3.1 TERMS

Adverse Event	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether related to the investigational device or not.
Case Report Form	Set of printed, optical, or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the Clinical investigation plan.
Clinical Data	Information concerning safety or performance that is generated from the use of a device and is sourced from the following: 1) clinical investigation(s) of the device concerned, 2) clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated, 3) reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated, 4) clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.
Clinical Investigation	Any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.
Clinical Investigation Plan	A document (protocol) that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organization and conduct of a clinical investigation.

Device Deficiency	Any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
Ethics Committee (In Norway REK)	An independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organizations.
Informed Consent	A subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the clinical investigation.
Investigational Device	A device that is assessed in a clinical investigation.
Investigator	An individual responsible for the conduct of a clinical investigation at a clinical investigation site.
Serious Adverse Event	Any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalization or prolongation of patient hospitalization, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;. NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.
Sponsor	Individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation.
Subject	Individual who participates in a clinical investigation.

3.2 ABBREVIATIONS

CIP	Clinical Investigation Plan
CRF	Case Report Form
DPIA	Data Protection Impact Assessment
DMP	Data Management Plan
DMR	Data Management Report
EEA	European Economic Area
GCP	Good Clinical Practice
IB	Investigator Brochure
ISF	Investigator Site File
NCA	National Competent Authority
NCI	National Coordinating Investigator
NoMA	Norwegian Medicines Agency
PI	Principal Investigator
REC	Regional Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File

4 BACKGROUND

The clinical investigation shall be carried out in accordance with the most recent version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

As an EEA-country, Norway has similar regulations as the EU. Clinical investigations of medical device(s) are regulated under the Medical Device Act LOV-2020-05-07-37 and related regulations (Norway). This act is valid from 26 May 2021. Clinical investigations started under previous regulation may continue, however reporting of serious adverse events and device deficiencies should follow LOV-2020-05-07-37.

Clinical investigations shall follow the harmonized standard NS-EN ISO 14155:2020, Clinical investigation of medical devices for human subjects – Good clinical practice. This document can be purchased online, the standard is reflected in this document.

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 (NoMA). If the sponsor's institution has a section for innovation or has established a cooperation with a Technology Transfer Organisation (e.g. Inven2, VIS, NTNU TTO), it can be useful to cooperate with them in this matter.

5 GENERAL

- A clinical investigation shall be conducted for one or more of the purposes:
  to establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for its intended use and achieves the performance intended
- to establish and verify the clinical benefits of a device
- to establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.

Before a clinical investigation is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual subject and society. A clinical investigation shall be initiated and continued only if the anticipated benefits justify the risk. The clinical investigation should be designed to confirm the benefit-risk analysis of the investigational device as outlined in the risk management report.
A justification shall be provided in the Clinical Investigation Plan (CIP).

The facilities where the clinical investigation is to be conducted shall be suitable for the clinical investigation and shall be similar to the facilities where the device is intended to be used.

5.1 RISK MANAGEMENT

Risk management activities shall be performed before and throughout the clinical investigation.

For both the clinical procedure and the clinical investigation process, the sponsor shall establish risk acceptability threshold, and predefine actions to be taken if thresholds are reached or exceeded. The risks shall be evaluated in accordance with ISO14971 - Application of risk management to medical devices.

A summary of the benefit-risk analysis shall be disclosed in the relevant clinical investigation documents. The residual risk, including the characterization of their nature (hazards), incidence (occurrence), severity and outcome (harms) shall be disclosed in the Investigator's Brochure (IB) and the instructions for use. The level of detail necessary shall be determined by the sponsor and managed in the interest of subject safety.

The CIP shall include all anticipated adverse device effects and a rationale for the related benefit-risk ratio

5.2 ROLES, RESPONSIBILITIES AND DISTRIBUTION OF TASKS

The main roles in clinical investigations of medical devices are;
- Sponsor,
- Cooperating institutions,
- Investigator(s) (National Coordinating Investigator / Principal Investigator in single centre investigations, NCI/PI),
- Study site staff and
- Monitor.

A short description of the roles, responsibilities and tasks are given below, as well as further outlined in the document "Roles and responsibility for Clinical Investigations of medical device".

An agreement must be in place prior to commencement of the clinical investigation where roles and responsibilities are defined. It shall among others ensure that any serious adverse events or any other reportable events are reported by the investigator or investigators to the sponsor in a timely manner.
An agreement to financing (may be separated from agreements on responsibilities) and disclosure of interest shall also be documented. Financial disclosures shall be archived both in the sponsor file and the site file.

5.3 SPONSOR

The sponsor is an individual or organisation taking responsibility and liability for the initiation or implementation of a clinical investigation. Even though the institution is sponsor for the investigation, the funding may come from external sources as well as from internal sources.

The sponsor holds legal responsibility for the study. In hospitals, this responsibility is often delegated from the CEO to department or clinic level ensuring that the responsibility is not too distant from the operative part.

The sponsor responsibilities are detailed in NS-EN-ISO14155. Many sponsor tasks may be delegated to the NCI/PI of the study, but the ultimate responsibility for the quality and integrity of the clinical investigation shall reside with the sponsor.

It is the sponsor's obligation to assure responsibilities and tasks follows Good Clinical Practice (GCP) (NS-EN ISO14155), the medical device act and the ACT 2008-06-20 no. 44: Act on medical and health research (Helseforskningsloven).

If additional institutions or parties are involved in the clinical investigation, the sponsor must ensure that an agreement between the parties are in place prior to study start.

5.4 COOPERATING INSTITUTIONS

Several institutions, both national and international, can be involved in the investigation. The clinical investigation may be planned as a multicenter study, where the study is conducted according to a single CIP and takes place at two or more investigational sites, regardless of location. Other cooperating parties may include for instance external laboratories.

5.5 NATIONAL COORDINATING INVESTIGATOR

If the study is conducted in several centres internationally, a National Coordinating Investigator (NCI) will be assigned in each country.

If the study is conducted in several sites in Norway, the NCI act as the project manager for all study sites. The National Coordinating Investigator is usually the Principal Investigator at one of the study sites although this is not a requirement.

The NCI is responsible for all communication with the Regional Ethics Committee (REC); application, amendments, reporting during the study (if applicable) and end of study notification. The NCI must ensure that a written and dated approval/favourable opinion for the clinical investigation is obtained from REC, as well as a notification to or approval from the National Competent Authority (NCA) (for Norway NoMA), before recruiting subjects.

In investigator initiated clinical investigations, several sponsor tasks may be delegated to the NCI as described in Roles and responsibility for Clinical Investigations of medical device.

If the sponsor is not resident in the country in which the clinical investigation is to be carried out, sponsor may delegate to the NCI to establish the country-specific requirements related to the research study and select a local representative who acts as the sponsor fulfilling responsibilities of the sponsor in that country.

5.6 PRINCIPAL INVESTIGATOR

The Principal Investigator (PI) is responsible for implementing and managing the conduct of the clinical investigation at a specific site, hospital, or other institution.

A clinical investigation may be conducted only where the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner or any other person entitled by national law to provide the relevant patient care under clinical investigation conditions.

Following the ISO14155, the Principal Investigator must document sufficient competency evidenced through CV or other relevant documentation, to lead and conduct the investigation in question at site. The PI shall moreover disclose any potential conflicts of interests, also financial.

The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the principal investigator in which case, he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

In single centre investigations the PI will have the responsibilities held by both the National Coordinating Investigator as described in chapter 5.1 as well as the responsibilities and tasks listed below.

The PI responsibilities is detailed the internal roles and responsibilities, if applicable, and in NS-EN-ISO14155.

5.7 STUDY STAFF

The Principal Investigator may delegate tasks to named staff within the institution that will be contributing to the investigation and/or subcontract tasks to cooperating partners. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training, or experience in the relevant medical field and in clinical research methodology, to perform their tasks. The delegation must be documented in the delegation log appendix 3 MU App03 Delegation Log. Only defined tasks can be delegated, not the responsibility

The Principal Investigator has the responsibility to ensure that the investigational staff members have sufficient competence to conduct their delegated tasks.

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

5.8 MONITOR

Clinical investigation of medical devices must have a person (monitor) responsible for overseeing the progress of a clinical investigation and to verify that it is conducted, recorded, and reported in accordance with the approved CIP and subsequent amendment(s), written procedures, NS-EN ISO 14155, and applicable regulatory requirements. Monitoring shall be conducted according to a monitoring plan or as agreed for a certain clinical investigation. The extent and nature of the monitoring, including the strategy for source data verification versus centralized data review (evaluation without visiting the investigation site), subject protection and timely reporting, shall be based on the objective, design, complexity, size, critical data points and endpoints of the clinical investigation and the degree of deviation from normal clinical practice. A risk-based monitoring approach may be used.

The monitor receives assignment from the sponsor and can be internal or external but cannot be any of the investigational staff involved in the investigation in question.

The procedures to be followed before, during and after the clinical investigation shall be described in the monitoring plan. The content of the monitoring plan shall follow the requirements set out in ISO14155. A template is available as described in chapter 7.13 Monitoring.

5.9 OUTSOURCING DUTIES OR FUNCTIONS

The sponsor may transfer duties and functions related to the clinical investigation, including monitoring, to an external organization (contract research organization, CRO), but the ultimate responsibility resides with the sponsor. The sponsor shall ensure oversight of any clinical investigation-related duties and functions. Any or function transferred to an external organization shall be specified in written agreements. Records of transfer of duties and functions shall be maintained.

5.10 COMPUTERIZED SYSTEMS

If computerized systems are used in the clinical investigation, they shall be validated for its use following a written procedure for computerized systems validation. The procedure shall at least cover the requirements set out in ISO14155 section 7.8. These requirements are applicable to any electronic records, including electronic CRFs,

electronic systems used for entering and processing data from paper CRFs received from sites and other electronic systems required in the clinical investigation.

6 PREPARING THE CLINICAL INVESTIGATION

When having identified the roles and distribution of tasks, the required documentation must be prepared and sent to REC and NCAs in the respective countries involved. All clinical investigations shall be reviewed by an ethics committee in accordance with national law. The process for application is further described in chapter 6.6.3 and 6.6.4.

The clinical investigation shall be designed and conducted in such a way that the rights, safety, dignity, and well-being of the subjects are protected, and the safety of the subjects should prevail over all other interests. Regardless, any clinical data generated from a clinical investigation shall be scientifically valid, reliable, and robust.

6.1 DEVELOPING CLINICAL INVESTIGATIONAL PLAN

A detailed study protocol (Clinical Investigational Plan, CIP) shall be developed, clearly outlining the objectives and endpoints of the clinical investigation. The CIP shall reflect the latest scientific and technical knowledge, and the investigation shall be designed to confirm or refute claims regarding the safety and/or performance of the device in question. The primary endpoint shall be appropriate to the device and clinically relevant.

The clinical investigation shall include an adequate number of observations to guarantee the scientific validity of the conclusions and be performed in a clinical environment that is representative of the intended normal conditions of use of the device.

The CIP must be version controlled and signed by sponsor and NCI/PI. The setup of the CIP for human research shall follow ISO14155 Annex A. It is recommended that the Transcelerate protocol template is used. A description is found in guidance for access.

6.2 DEVELOPING INVESTIGATOR'S BROCHURE (IB)

The purpose of the IB is to provide the principal investigator and the investigation site team with sufficient safety and performance data from pre-clinical or clinical investigations to justify human exposure to the investigational device specified in the CIP. The IB shall be updated in case of design changes or new information concerning safety or performance. The content of the IB is specified in Annex B of ISO14155.
The IB shall ensure that the device fulfils the basic requirements in the regulation, except for the objectives of the investigation. To document how the general safety and performance requirements of the MDR are met, Annex I of the MDR may be used.

6.3 DEVELOPING SUBJECT INFORMATION SHEET AND CONSENT FORM

All participants in the clinical investigation must receive both written and verbal information about the investigation and given ample time to consider whether to consent and take part in the clinical investigation. The subject information sheet and consent form should be developed based on REC's templates (National differences may

occur) and be approved/receive opinion by REC before it is used. The content should be easily understood by the subjects in the investigation (lay people) and, as a general rule, the participants should sign and date the consent form themselves. Special considerations shall be taken for vulnerable population i.e. children or subjects not able to consent themselves.

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/opinion before being used. In urgent cases, e.g. where new safety information is available that requires immediate action, subjects should be informed verbally before the written documents are available.

All consents (written or verbal) should be documented in the patient's medical record.

Informed consent process
The informed consent process must be described in the protocol and be provided by a member of the investigation team who is appropriately qualified. The information given must be kept comprehensive, concise, clear, relevant, and understandable to the subject or legally delegated representative. Informed consent shall be written, dated, and signed by the person performing the interview and by the subject or legally designated representative. Special attention shall be paid to the information needs of specific patient populations and subject needs, as well as the methods used to give the information

The subjects must be informed that they have the right to refuse to participate without having to justify. The subjects may withdraw from the clinical investigation at any time, without any resulting detriment and without having to provide any justification. The withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

A written consent must be obtained before any specific procedures for the investigation are initiated. An investigational 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.

For a Clinical Investigation for medical device the following must be added to the general informed consent template:

- If the device under investigation is an implant, data shall be kept for at least 15 years after the investigation has ended. All other devices at least 10 years.
- The data collected in the study, as well as the subject medical records, shall be made available to monitors and regulatory authorities upon request. (Suggested text for this can be found in in the REC template for drug trials)

6.4 INSURANCE

The application/notification to the Norwegian Medicines Agency (or other NCAs as applicable), 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 participating subjects in Norway are covered through NPE, but a confirmation is required. The confirmation can be obtained by emailing NPE.

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

6.5 ADDITIONAL REQUIRED DOCUMENTATION

NoMA requires additional documentation than the abovementioned to be provided to demonstrate fulfillment of the general safety and performance requirements of the regulation. The documentation to provide shall among others include a risk assessment and declaration of compliance with the Medical Device Act. A complete list of documentation to submit can be found on the NoMA homepage.

6.6 APPROVALS/ NOTIFICATIONS PRIOR TO START OF THE INVESTIGATION

All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable, and appropriately stored to provide a complete history of the clinical investigation. Where relevant, the accuracy of translations shall be guaranteed and documented.

6.6.1 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.

When developing a device that will store personal data, early involvement of the information security officer is recommended

6.6.2 General Data Protection

An assessment to the applicability of the General Data Protection Regulation 2016/679 should be made. Typically, the assessment is conducted at the institution by evaluating whether a Data Protection Impact Assessment (DPIA) is needed, as well as to conduct a DPIA if required. The requirements depend on the nature of the clinical investigation and internal hospital routines. The evaluation shall be submitted to the dedicated department at the hospital prior to initiating the investigation.

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

All investigations under the scope of this procedure and the Medical Device Regulation require approval from the Regional Ethic Committee prior to start up. The submission to REC shall be done by the NCI using the electronic application form on the REC homepage.

The Clinical Investigation Plan and patient information sheet / patient consent form must be part of the REC application. Moreover, all written information to be provided to the participants during the clinical investigation i.e. questionnaires and adverts/recruitment material, must be approved by REC.

Ethics committee filings and approval
Information to be provided to EC, is detailed in ISO14155. There may be national variances informed under the ethics committee homepage, REC in Norway.

The EC approval or EC waiver from the investigator shall be archived in the sponsor- and site file.
If the Ethics Committee does not approve the clinical investigation, the investigation may not proceed until issues are resolved and approval/favorable opinion is obtained.

6.6.4 The Norwegian Medicines Agency

For clinical investigation where the device do not bear a CE-mark, or investigations outside the scope of intended purpose, an application shall be submitted to the relevant national authorities in the country in which the clinical investigation is to be conducted. The application and the required documentation to be provided is given under the NCA homepages i.e. NoMA in Norway.

For post market clinical follow-up (PMCF) studies within the CE marking, but where subjects are exposed to additional invasive or burdensome procedures, the sponsor shall notify authorities at least 30 days prior to commencement.

Note: Since the electronic system referred to in the Medical Device Regulation is not yet available, there may be national differences to required documentation, as well as about the notification requirement of PMCF studies. A single application in international studies is also not possible yet.

The NoMA will review the documentation and inform the sponsor of whether there are any objections to the initiation of the investigation. If the sponsor has not been notified within 60 days of the notification, the clinical investigation may commence. The NoMA may however inform the sponsor of its decision before the end of the 60-day period or request additional information. If additional information is requested, the 60-day time period will be put on hold until the requested documentation has been received. .

Information about documentation to provide with the application, is given under NoMAs webpage.

6.7 LABELLING, STORAGE AND ACCOUNTABILITY OF INVESTIGATIONAL MEDICAL DEVICE

If a device is intended for clinical investigation only, the following words must be on the label: “Exclusively for clinical investigations”. If the device is provided in a sterile condition, information on the packaging must be present. The medical device under investigation should always be stored in accordance with the manufacturer’s specification and out of reach of unauthorized personnel.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. Instruction shall be in place and the sponsor shall make packaging materials available, if applicable, for the safe return or disposal of investigational devices, including potentially hazardous devices. At any time during the clinical investigation, the location of any investigational device must be traceable, e.g. using appendix 4 MU App 04 accountability of medical device

Records to be kept by the investigator shall be described in the CIP.

6.8 REGISTER THE INVESTIGATION AT CLINICALTRIALS.GOV AND AT HOSPITAL WEB SITE

All clinical investigations on medical devices should be registered at ClinicalTrials.gov or other approved registry, prior to study start up. Such registration may be a prerequisite for publication of the study results later. Note that the registration process may take a few weeks, and it is imperative that the registration is completed prior to the commencement of the study

The Ministry of Health and Care Services in Norway has requested all clinical studies to be registered at the web site kliniskestudier.helsenorge.no. Studies are uploaded to this website from the official hospital web sites. Contact local research support at your institution for registration guidance.

6.9 STORAGE OF DOCUMENTATION AND ARCHIVING

All essential documents, which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced, must be archived. Filing essential documents at the investigator/institution and sponsor sites in a timely manner shall assist in the successful management of a clinical investigation by the investigator, sponsor, and monitor.

The files shall be established at the beginning of the clinical investigation, both at sponsor site and at the investigator site(s). The content of the files and timepoints the various documents should be documented and on file is described in the ISO14155 Annex E.

The sponsor is responsible for maintaining the sponsor file and prepare the investigator site file for all investigator sites.

Throughout the investigation all required documentation and correspondence shall be kept in the Investigator Site File (ISF) / local investigation archive and in the Trial Master File (TMF) /sponsor's study archive. The ISF should be available for all investigation staff. A combined ISF and TMF can be used for single centre studies. Templates for content of the ISF and TMF is available under the Appendices MU App 11 Table of Content ISF, MU App 12 Table of Content TMF and MU app 13 Table of Content ISF TMF combined.

When the investigation is completed (all subjects have completed last visit) and the investigation report and publication is available, the investigation documentation should be archived (TMF, ISF). The TMF for non-CE marked devices should be kept for at least 15 years for investigations involving an implantable medical device and 10 years for all other medical devices. There are no regulated requirements for how long the ISF should be kept. A list of documents that should be maintained is provided in Annex E of ISO14155.

6.10 CHANGES TO THE CLINICAL INVESTIGATION AFTER APPROVAL

If changes to the clinical investigation are required after approval, an updated revision (with revision number) and amendment form, must be sent to REC for approval before the changes can be implemented. This is described in the Health Research Act § 11 and on the Regional Ethics Committee homepage. Some changes are not considered substantial and do therefore not need approval prior to the change(s). These exemptions are detailed on the REC homepage. Changes to the relevant documentation shall be clearly identifiable. The process for modifications shall be described in the protocol.

Changes that are required to ensure subject 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.

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 REC approved study end date.

All substantial amendments to the clinical investigation should also be notified to the NoMA and a response must be received before implementing the change(s). Changes may be implemented at the earliest 30 days after the notification unless the changes are refused by the Member State(s) and has issued a negative opinion in relation to the changes/modification of the clinical investigation.

Note: The notification shall proceed within one week, by means of the electronic system referred to in Article 73. The electronic system is not yet available. The reporting to the Member States through the electronic system will not be applicable before Eudamed is launched.

7 CLINICAL INVESTIGATION EXECUTION

It shall be ensured that the following areas are addressed:
a) accountability of investigational devices throughout the clinical investigation,

b) documenting correspondence with all parties involved in the clinical investigation, including ethics committees and regulatory authorities,

c) ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation,

d) ensuring that risk management activities are performed and documented throughout the clinical investigation

e) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s)

f) taking prompt action to secure compliance with all clinical investigation requirements,

g) performing and documenting root cause analysis and implementation of appropriate corrective and preventive action if noncompliance significantly affects or has the potential to significantly affect subject protection or reliability of clinical investigation results,

h) submitting progress reports after the data integrity is confirmed, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities.

7.11 SPONSOR AND INVESTIGATOR OBLIGATION

The sponsor and investigator shall ensure that the clinical investigation is conducted in accordance with the approved clinical investigation plan (protocol).

It is the sponsors responsibility to keep available for the competent national authorities any documentation required by the MDR.

7.12 SITE PERSONNEL TRAINING

After all approvals are obtained and the investigation may start, the PI in each participating site must ensure that the investigational staff is trained in all applicable study procedures. The training documentation; e.g. meeting agenda, minutes/report, participants, agreed delegation of tasks should be archived in the Trial Master File (TMF) (index for multi- or single centre investigations) and in the Investigator Site File (ISF). It is recommended to have regular team meetings with minutes to be archived in TMF with a copy to ISF.

7.13 MONITORING

Sponsor shall dedicate a monitor to oversee the conduct and progress of the investigation, with special attention to the participant's rights, safety, and well-being, as well as data quality and documentation according to the regulation. A monitoring plan, should, generally, be available at the start of the investigation. Depending on the structure of the device study, the monitor shall conduct regular visits and report to the sponsor in a customised monitoring report. Monitor should perform a site initiation visit before the study can start. Templates for monitoring of medical device studies are available as appendices to this SOP (Appendix 15 Initiation Report MU, Appendix 16 Monitoring Report MU, Appendix 17 Close-Out Report MU). Monitoring is further detailed in NS-ISO14155 and SOP LM2.14 Monitoring (for drug trials).

Internal and external inspection
The sponsor shall provide evidence that the investigation is being conducted in line with good clinical practice, for instance through internal or external inspection.

7.14 HANDLING AND STORAGE OF RESEARCH DATA

All clinical investigation information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection. Appropriate technical and organizational measures shall be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, where the processing involves transmission over a network. *Authorities* may inspect investigation site(s) to check that clinical investigations are conducted in accordance with the requirements of the regulations and with the approved investigation plan.

All investigational data must be captured without direct identifiable personal information. All subjects assessed/screened for investigation participation and who have signed a consent form should be registered and pseudonymised using Screening Log. All subjects included in the investigation will have a study number generated that will follow the collected data (questionnaires, CRF etc.). An identification and enrolment log should be completed, connecting the subject number to the subject identification must be kept ensuring access only for delegated personnel.

Subject data are recorded in a Case Report Form (CRF) specific for the investigation and 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 (e.g. web based) or on paper. A suggested list of CRF content is available in Annex C in the ISO14155. Development and completion of CRFs are further described in the procedure LM2.11 Case Report Form (CRF) and Patient Reported Outcome (PRO) Form Management (for drug trials).

The sponsor must ensure access to proper statistic competence and systems for registering data, data handling and storage of data and samples. The institutions procedures for safe storage of data for research shall be followed.

Data Management Plan
Data handling should either be described in the Clinical Investigational Plan or in a separate data management plan by adjusting Data Management Plan (DMP). The data management plan (DMP) describes the methods used to collect, enter, validate, transfer and process clinical data in the trial. Any changes to the DMP after approval shall be reflected in the Data Management Report (DMR).

The database must be locked prior to analysing the data. A template is available in the LM SOP, Database Lock prior to analysing the data.

Data management is further described in NorCRIN SOP LM 2.10 for drug trials.

Statistical Analysis Plan (SAP)
The description of and justification for statistical design and analysis of the clinical investigation shall be described in a statistical analysis plan, if applicable, or if deemed appropriate thoroughly described in the CIP.

7.15 REQUIREMENT FOR SOURCE DOCUMENTS

As a ground rule any data collected in a clinical investigation must be documented in the subjects' medical records or other source document. In this way the data can be reconstructed if needed.

7.16 REPORTING

Each Principal Investigator must follow the internal reporting procedures in their own institution. In addition, the PI/NCI is responsible for reporting to regulatory authorities. PI is moreover responsible for reporting study status, progression and any serious adverse events or adverse device event to sponsor and internally according to the institution's routines.

7.17 REPORTING SERIOUS ADVERSE EVENTS (SAE) AND DEVICE DEFICIENCIES

The guidance MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 should be used for reportable adverse events and device deficiencies and the process for reporting shall be described in the CIP.

All Serious Adverse Events and any Device Deficiency that might have led to an SAE must be reported by investigator to sponsor immediately, but no later than 3 calendar days after awareness of the event.

The sponsor shall report without delay to all Member States in which the clinical investigation is being conducted, all of the following:
(a)any serious adverse event that has a causal relationship with the investigational device, the comparator, or the investigation procedure or where such causal relationship is reasonably possible;

(b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
(c) any new findings in relation to any event referred to in points (a) and (b).

Sponsor must then report to NOMA immediately but no later than 2 calendar days after awareness of all reportable events as which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it. Any other reportable events or a new finding/update should be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor about the new reportable event or of the new information in relation to an already reported event.

SAEs shall be reported to NoMA using the guidance safety report form.

Eudamed, an electronic system on clinical investigations, will be implemented as SAE reporting channel for all new SAEs once implemented, expected 2022.

A ground rule is to report any reportable events immediately.

Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all information referred to above.

The period for reporting shall take account of the severity of the event and follow the reporting requirements as given by the 10-1 MDCG 2020-10-1 Guidance on safety reporting in clinical investigations for SAE reporting and be detailed in the CIP.

Clinical investigations conducted on CE marked devices, shall follow the process for incident reporting unless otherwise required. The reporting of serious adverse events or device deficiencies during clinical investigations and the reporting of serious incidents occurring after a device has been placed on the market should be clearly distinguished to avoid double reporting.
Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

The sponsor shall also report to the Member States in which the clinical investigation is being conducted any event that occurred in third countries in which a clinical investigation is performed under the same clinical investigation plan as the one applying to a clinical investigation covered by the MDR.

The reporting of events to the member states as outlined in this chapter, shall apply where a causal relationship between the serious adverse event and the preceding investigational procedure has been established. Serious adverse events with no causal relationship to device or investigational procedure are not required to be reported.

Signals from adverse events or device deficiencies that might indicate a serious health threat can be detected by either the sponsor or principal investigator but are evaluated by the sponsor. Any occurrence of a serious health threat can require a specific reporting process according to regulatory requirements.

7.18 DEVICE DEFICIENCIES

Device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer; All device deficiencies of an investigational device shall be documented throughout the clinical investigation and managed in accordance with written procedures for the control of a non-conforming product.

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect shall be reported as specified in chapter 7.17.

Return of devices involved in the device deficiency
The sponsor is responsible for initiating the return of devices involved in the device deficiency. It shall be communicated to site how the returning shall proceed. The principal investigator shall document the return in the accountability log at site.

7.19 END OF STUDY, TERMINATION OR TEMPORARY HALT

The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time is set out in the clinical investigation plan. Sponsor shall notify each Member State in which a clinical investigation was being conducted of the end of that clinical investigation in that Member State. That notification shall be made within 15 days of the end of the clinical investigation in the individual country.

If the sponsor temporarily halt or terminates a clinical investigation early, it shall inform the involved Member States within 15 days providing a justification. If the clinical investigation is temporarily halted or terminated on safety grounds, all Member States in which the clinical investigation is being conducted shall be informed within 24 hours.

Note: this will go through the electronic system, but not yet established

7.20 CLINICAL INVESTIGATION REPORT

A clinical investigation report shall be written after study close-out. Appendix 14 MU App 14 Trial Report specifies the required content of the report. The report shall be made available for review by the NCI and all PIs. The clinical investigation report shall be signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings.

The final study report shall be maintained. Irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, sponsor shall submit to the Member States in which a clinical investigation was conducted a clinical investigation report. The clinical investigation report shall be accompanied by a summary presented in terms that are easily understandable to the intended user. Both the report and summary shall be submitted by the sponsor.

Note: Report and summary will in the future be sent to the electronic system. Electronic system not available yet.
Note 2. The Commission shall issue guidelines regarding the content and structure of the summary of the clinical investigation report. In addition, the Commission may issue guidelines for the formatting and sharing of raw data, for cases where the sponsor decides to share raw data on a voluntary basis. Those guidelines may take as a basis and adapt, where possible, existing guidelines for sharing of raw data in the field of clinical investigations.

Note 3: The summary and the clinical investigation report shall become publicly accessible through the electronic system, at the latest when the device is registered and before it is placed on the market. In cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission. If the device is not registered within one year of the summary and the report having been entered into the electronic system, they shall become publicly accessible at that point in time

Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation, it shall be submitted as soon as it is available. In such case, the clinical investigation plan shall specify when the results of the clinical investigation are going to be available, together with a justification.

The Clinical Investigation Report shall be made available upon request to any Investigator or Ethics Committees for a particular study. If a reviewer does not agree with all or part of the clinical investigation report, his/her comments shall be recorded and communicated to the other Investigators.

If required, the report shall be signed by both the sponsor and the NCI. Even if the clinical investigation was terminated prematurely, a report shall be written. A final report shall be sent to NoMA, as well as an end of study notification to REC.

7.21 DISPOSITION DEVICE

Sponsor shall ensure completion of device disposition according to the study protocol and research agreement. Disposition of the device and related materials used in the clinical investigation shall be documented.

7.22 STUDY CLOSURE

Routine close-out activities shall be conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved, and all parties are notified. MU Appendix 17 Close-Out report MU may be used as also referred under chapter 7.13 Monitoring.

Certain national regulations can also require notifications to be done within specific timelines.

7.23 PUBLICATIONS

The results of the clinical investigation shall be published. The framework of publication of study results shall be given in the Clinical Investigation Plan.

8 HANDLING DEVIATIONS

Deviations to this SOP should be handled according to each institution’s procedures for non-conformances.

Deviations in the clinical investigation shall be handled as described in the CIP.

Serious or continuous non-compliance with the CIP or regulations

In the case of serious or continuous non-compliance with the CIP or regulations, whether at sponsor, by suppliers or at investigator sites, the sponsor shall determine the cause. It shall be considered terminating or suspending the participation of a particular investigation site or investigator, or agreement with suppliers, if it identifies serious or repeated deviations.

The sponsor shall establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation.

9 REFERENCES

9.1 NORMATIVE REFERENCES

Act on medical devices: Lov om medisinsk utstyr -LOV-2020-05-07-37 (Norwegian)
REGULATION (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
ACT 2008-06-20 no. 44: Act on medical and health research (the Health Research Act)
ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/home
MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745
kliniskestudier.helsenorge.no.
Norwegian Medicines Agency – Clinical investigation of medical devices (English) – Klinisk utprøving og evaluering av medisinsk utstyr and Medisinsk utstyr (Norwegian)
The Norwegian System of Patient Injury Compensation (English) – NPE (Norwegian)
NS-EN ISO 14155:2020, Clinical investigation of medical devices for human subjects.
NS-EN ISO 14971:2019 Medical devices- Application of risk management to medical devices
Oslo University Hospital (OUS) info regarding registration on ClinicalTrials.gov and helsenorge.no (Norwegian)
Regulations concerning organising of medical and health related research: Forskrift om organisering av medisinsk og helsefaglig forskning FOR-2009-07-01-955 (Norwegian)
REK. Regional Committees for Medical and Health Research Ethics. Available from: https://helseforskning.etikkom.no/reglerogrutiner/endringograpport?p_dim=35021&_ikbLanguageCode=us. (Accessed: 07.July 2020).

9.2 INTERNAL REFERENCES

Procedures:

- NorCRIN SOP LM 2.01 «Protocol» (for drug trials)
- NorCRIN SOP LM 2.09 «Study Files» (for drug trials)

- NorCRIN SOP LM 2.10 «Data Management» (for drug trials)
- NorCRIN SOP LM 2.11 «Case Report Form (CRF) And Patient Reported Outcome (PRO) Form Management» (for drug trials)
- NorCRIN SOP LM 2.14 «Monitoring» (for drug trials)

Appendices

- *MD Appendix 01 Retired*
- *MD Appendix 02 Retired*
- MD Appendix 03 «Delegation Log»
- MD Appendix 04 «Accountability of Medical Device»
- *MD Appendix 05 Retired*
- *MD Appendix 06 Retired*
- *MD Appendix 07 Retired*
- *MD Appendix 08 Retired*
- *MD Appendix 09 Retired*
- MD Appendix 10 «Guidance safety report form»
- MD Appendix 11 «Table of Content ISF»
- MD Appendix 12 «Table of Content TMF multicentre»
- MD Appendix 13 «Table of Content ISF-TMF combined single-centre investigation»
- MD Appendix 14 «Clinical Investigation report»
- MD Appendix 15 «Initiation Report MD»
- MD Appendix 16 «Monitoring Report MD»
- MD Appendix 17 «Close-Out Report MD»

10 REVISION HISTORY

Revision	Changes since previous revision	Author	Effective date
1.0	N/A	Anne Mathilde Kvamme	July 2017
2.0	Regulatory Authority for clinical medical device investigations changed from the Directorate of Health to The Norwegian Medicines Agency Update of MEDDEV 2.7/3 reference	Anne Mathilde Kvamme	Jan 2018
2.1	Clarification of Scope	Anne Mathilde Kvamme	Jan 2020

	Adding monitoring report templates as appendices		
3.0	SOP updated for minor typos and some information updated or added. Scope expanded to include proof of concept/feasibility studies. New chapter 5.5 Additional required documentation New chapter 6.6.2 GDPR Hyperlinks controlled. References checked and updated. SOP updated to comply with ISO14155:2020 and MDR regulation Reviewed by LINK Medical Research AS	Anne Mathilde Kvamme	May 2021