## 1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for application for approval and start-up of clinical trials.

For transition of trials approved according to the directives 2001/20/EC and 2005/28/EC (old legislation) to the Clinical Trial Information System (CTIS) according to Regulation 536/2014 see Working Instruction Transition from outgoing legislation to Reg 536/2014.

This SOP ensures compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP Legislation and Guidelines.

## 2 SCOPE

This SOP is valid for all clinical drug trials sponsored by hospitals that have implemented the NorCRIN SOPs.

## 3 RESPONSIBILITIES

Sponsor is responsible for ensuring that for all clinical drug trials approvals are obtained and that the trials are started in accordance with this SOP.

For multicentre trials, the sponsor has overall responsibility for ensuring written agreements with cooperating healthcare companies / other partners.

The sponsor's responsibilities shall be described in the quality system of his/her institution. Tasks are delegated according to SOP Roles and Responsibilities in clinical trials implemented in the institution.

The sponsor is responsible for obtaining approval of a clinical drug trial by ethics committees and competent authorities and other concerned bodies.

The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf. Transfer of duties shall be specified in a written agreement.

## 4 PROCEDURES

The application for a clinical trial consists of Part I and Part II. Part I is assessed by the competent authorities and possibly the ethics committees (ECs). Part II is assessed by EC only. In Norway, Part I will be assessed by the Norwegian Medicines Agency (NoMA/SLV) and Part II by Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

For clinical trials with medicinal products (MPs) that contain or consist of genetically modified organisms (GMO-MPs) for use in humans, application must be sent both in CTIS and to GMO@legemiddelverket.no, see

Clinical trials with GMOs in medicinal products - Norwegian Environment Agency.

Genetically modified micro-organisms (including viruses, viroids, animal and plant cells in culture) may have to be carried out under containment until given to the patient, to limit contact of these organisms with the environment. Such activities include for example the process of genetic modification, the use, storage, transport, destruction and disposal of GM microorganisms. NoMA (SLV) will involve the Health Directorate to assess whether approval for contained use is required. For details see Genterapi - Helsedirektoratet

## 4.1 Application in the EEA

### 4.1.1 Required documents

Annex I of REGULATION (EU) No 536/2014 lists the required documentation. Part I consists of sections B to J and Q, and Part II of sections K to R. The European commission has also prepared a Q & A document to complement the regulation. To keep track of the documentation, use of the Sponsor Checklist Planning of Clinical Trial is recommended. For international trials, see working instruction International Trials.

The documents should be signed and archived in Trial Master File/Investigator Site File (TMF/ISF). Redacted or unsigned versions of the same documents should be uploaded in CTIS.

The document naming convention issued by the Clinical Trial Coordination Group (CTCG) should be followed.

The following SOPs and templates are useful for Part I:

- SOP Protocol
- SOP Investigational Medicinal Product (IMP) at Trial Start
  Template statement on compliance Regulation (EU) 2016/679 Language requirements for part I documents can be found in the Q & A document, Annex II

The following SOPs and templates are useful for Part II:

- SOP Preparing Written Information and Consent Form. In Norway, if the template from REK is not used, the sponsor should attach documentation confirming that all requirements in Regulation (EU) No 536/204 are covered.
- The European Commission has provided guidance for submission of Part II documents, Part II Document Harmonisation Guidance, which includes information about:
  - Investigator CV (template). To be issued by PI.
  - Site and Facilities Suitability (template). To be issued by the head of the clinic/institution or equivalent, according to institutional procedures
  - Declaration of Interest (template). To be issued by PI. To be uploaded in the Suitability of the investigator section.
  - List of Participating Sites, including number of participants per treatment arm. To be uploaded in the Suitability of the investigator section (naming M3_List of Participating Sites).

- Informed consent and patient recruitment procedure (template). In Norway, the trial subject should not be in a dependent relation to the person who asks for the subject consent. Subjects that do not understand Norwegian should in general not be excluded from inclusion and should be given written and oral information in a language they master. For translations, see Oversettelsestjenester - Sykehusinnkjøp (sykehusinnkjop.no).
- Compensation for trial participants (template) and
- Compliance with applicable rules for biological samples (template)
- Template statement on compliance Regulation (EU) 2016/679

If the templates are not used, a separate document should describe where the different items are covered.

For guidance on special subject groups, see Veileder til helseforskningsloven. The study subjects should feel free to be in included in the study without any penalties. The site should therefore be conscious about the possible dependency between investigator and study subjects and plan recruitment procedure thereafter, e.g. involving other staff members. Alternatively the CI should explain in the application why this is not possible and how to safeguard the study subject's free decision.

All subject questionnaires that are linked to in the protocol under Part I application must be uploaded as separate documents under the heading "Subject information and informed consent form", Part II application. The uploaded questionnaires must hold the same language as it is presented to the subjects that are participating in the study.

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Insurance: In Norway insurance should be purchased through Legemiddelansvarsforeningen. The coordinating investigator will ensure payment of the premium before the trial is initiated, and then every year as long as the trial is in progress.

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### 4.1.2 Application process

For submission of application for clinical trials in all EEA-countries, Regulation 536/2014 applies.

#### 4.1.2.1 Roles

Coordinating Investigator (CI) must follow the institution's procedure in order to get an EU CT number and applicable roles in Clinical Trial Information System (CTIS).

Persons given "CT admin" rights will be able to assign roles to other qualified persons as appropriate for the trial.

In order to do that, the future user should request a role in CTIS in the same way the CT admin did, but now the CT admin for that specific trial will be able to assign the roles.

The future user will need to:

1. Get an EMA account. See EMA Account Manager.
2. Log on to CTIS, click https://euclinicaltrials.eu/home

3. Select name at the upper right corner → Personal profile → Update employer information → choose the appropriate institution. Check the institution's procedure to ensure the right organization number and address is chosen.
4. Select name at the upper right corner → My roles → Request role → select your organization, scope= specific_trial, enter EU CT number provided by CT Admin, select appropriate role. Several roles can be requested.
5. The CT admin will then need to log on to CTIS and approve the roles (select "User administration" on the blue line → Search → select persons for whom roles should be approved → Approve → Confirm)

Alternatively, the CT admin can assign roles without the users requesting them, but their user ids must be known by the CT admin.

Roles can be assigned for different parts of the application and further correspondence within CTIS: Part I, Part II, notifications, CT (both parts and notifications), Q-IMPD (the manufacturing part of the IMPD). Roles are also assigned at different levels; viewer, preparer (will also be able to view) and submitter (will also be able to view and prepare).

In order to be able to submit Annual Safety Reports (ASRs), a specific "ASR submitter" role must by applied for.

CTIS - M03 Registration of a new CTIS user - YouTube

If the trial is to be conducted in several institutions, CI should require that the unregistered institutions get registered in the EMAs OMS database, see Clinical Trials Information System (CTIS) - Sponsor Handbook, section 3.2.1. The registration process can take up to 10 days.

As CTIS is a closed system that does not send information by emails, it might be useful to add a user whose task is to monitor the system for replies or requests for information (RFIs).

#### 4.1.2.2 Application

See EMAs Training program, especially module 10.

Common rules:

- All field with asterisks should be filed in.
- The lock should be closed when editing (and open when submitting the application).
- Documents should be uploaded as PDFs
- Most documents will be made publicly available. It is specified in CTIS for each single section. The first uploaded document will always be the one "for publication". "Not for publication" documents should be uploaded under the first document.
- Documents "not for publication" can be uploaded by clicking "add document"
- In order to comply with GDPR, the use of personally identifiable information such as date of birth, signature, home address, children names, photographs etc. should be avoided. Use of Investigator CV (template) is recommended.

The submission information is under four different tags: Form, MCSs, Part I and Part II. Under "Form", a declaration of compliance with Regulation (EU) 2016/679 should be provided. The EU commission is working on a template, but for the moment the following sentence has proven acceptable in national trials: "*The Sponsor, insert name of the sponsor institution, or his or her representative will process all applicable data in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) (the "Data Protection Legislation").*" In national trial, it is not necessary to upload the document in Part II.The template mentioned under 4.1.1. should be used. The form should also state how long the research activity, including analyses of biobanks and all publishing based on the trial data, is going to last. The same document can be used under Part II.

The CI should propose one of the member states concerned as reporting member state (RMS). For national trials the Norwegian Medicines Agency (NoMA/SLV) shall be the RMS. For a low-intervention clinical trial, where the IMP is not used in accordance with the terms of the marketing authorisation (MA) but the use is evidence-based, a member state where the use is evidence based, should be proposed as RMS.

If a commercial company has provided documents such as e.g. an Investigator's Brochure to be used in the application, the CI should ask/review the contract with the company in order to check whether the company requires deferrals (request for postponing publication) for their documents.

The application process is detailed below:
Green: Coordinating investigator (CI) - Blue: Reporting Member State (RMS) - Red: Member State (MS)

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| Validation | Within 6 days from submission, RMS shall notify CI of any change in RMS if applicable |
| | Within 10 days from submission, RMS shall notify the sponsor of the following:<br>(a) whether the clinical trial applied for falls within the scope of this Regulation;<br>(b) whether the application dossier is complete<br>If no notification is given, the application will be considered as complete and valid → Validation date |
| | Within 10 days from notification (Request for Information (RFI)) from RMS, CI shall comment or complete the application<br>If no comments are provided, the application shall be deemed to have lapsed in all MS |
| | Within 5 days from receipt of comments, RMS shall accept or not the application → Validation date |
| Assessment part I | RMS shall assess:<br>- whether the trial is low-intervention or not<br>- Part I documentation |
| | If RMS does not require additional information:<br>Within 45 days from validation date, RMS shall inform the sponsor about the conclusion of the assessment<br>This period is extended to 95 days for advanced therapies or medicinal products developed by means of recombinant DNA technology or controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma and monoclonal antibody methods.<br>→ Reporting date. |
| | If RMS requires additional information: |

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| | RMS may request additional information from the sponsor between validation and reporting date (RFI sent to Sponsor, visible at the front page in CTIS).<br>By the due day (maximum 12 days) of request, CI shall submit requested information<br>Within maximum 76 days (or 126 days) from validation date, RMS shall inform the sponsor about the conclusion of the assessment → Reporting date |
| Assessment part II | Each MS shall assess Part II documentation |
| | If MS does not require additional information:<br>Within 45 days from validation data, each MS shall submit the assessment report to the sponsor (CI) → Reporting date |
| | If MS requires additional information:<br>MS may request additional information from the sponsor between validation and reporting date (RFI sent to Sponsor).<br>Within the due date (maximum 12 days) of request, CI shall submit requested information<br>Within maximum 76 days from validation date, MS shall inform the sponsor about the conclusion of the assessment → Reporting date |
| Decision | Within 5 days from reporting date or last day of the assessment, MS will notify sponsor about the decision → Notification date<br>If MS does not notify, the conclusion on Part I of the assessment report shall be deemed to be the decision of MS |
| Expiry | Within 2 years from notification date, if no subjects have been included then the authorisation shall expire in the MS |

Please note, if the timelines are not met, the application will be cancelled in CTIS.

#### 4.1.2.3 Responses to RFIs

It is recommend to state references/explain if changes have been made in the submitted documentation. Furthermore, changes should be submitted as both a track-changes version (as supportive documentation to the RFI response) and a clean version (as part of the trial dossier in part I). Please use the ”change application” functionality, when you have done changes to the dossier (IMPD, protocol, IB etc.).

In case a document (e.g. protocol) needs to be changed, this should be done from the correct placeholder by using the “update” button. This will ensure correct versioning and publication in accordance with deferral/transparency rules. The add document button next to the response to RFI, should only be used in case you have supportive documentation to justify your response.

#### 4.1.2.4 How to manage RFIs

- Relevant videos:How to manage the workload in CTIS – RFI tab: where to find RFIs and sort them
- How to respond to RFI considerations and submit an RFI response; how to respond, uploading supporting documents and submission

- How to change a Clinical Trial Application as part of an RFI response

See also FAQs.

All responses to RFIs need to be summarised in a document that is uploaded at the top of the RFI. The summary should detail all changes made to documents and especially information given in the consideration answers and not included in other documents.

### 4.2 Application outside EEA

Similar documentation will be required in non-EEA countries as in EEA-countries. CI should seek information about application process.

Information should be gathered by using the Feasibility Questionnaire Template. See also Working Instruction International Trials. See also Working Instruction for international trials.

### 4.3 Registration

CTIS is not yet a primary registry for trials and registration in clinicaltrials.gov is therefore required. The trial should also be published on the hospital's website once the trial is approved and ready for recruitment, according to local procedure.

### 4.4 Start-up

Approval from the competent authority and ethics committee is a pre-requisite for initiation of the trial. It is recommended that the Start-up Meeting Checklist and the template Start-up Meeting Agenda are used to ensure that all requirements are complied with and all decisions are documented.

## 5 DOCUMENTATION

All documentation submitted for approval will be filed in the trial master file (see SOP Study Files).

## 6 NON-COMPLIANCE MANAGEMENT

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution. Protocol deviations should be reported according to the study protocol or the Protocol Deviation Handling plan.

## 7 REFERENCES

### 7.1 External References

- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) – in particular section 3.1, 4.1, 4.4, 5 and 6
- EudraLex-Volume 10.
- CTIS

- REGULATION (EU) No 536/2014 of The European Parliament and of the Council on clinical trials on medicinal products for human use, in particular chapter II and Annex I
- Veileder til helseforskningsloven (Guide to the Health Research Act; in Norwegian)
- Lov om produktansvar [produktansvarsloven] – LOV-1988-12-23-104 (Laws on product liability; in Norwegian)
- EMAs training program
- Part II Document Harmonisation Guidance, which includes information about:
    - Investigator CV
    - Declaration of Interest
    - Site and Facilities Suitability
    - Informed consent and patient recruitment procedure
    - Compensation for trial participants
    - Compliance with applicable rules for biological samples

### 7.2 Internal References

- SOP Protocol
- SOP Preparing Written Information and Consent Form
- SOP Investigational Medicinal Product (IMP) at Trial Start
- SOP Study Files
- Working Instruction International Trials

## 8 ATTACHMENTS

- Sponsor Checklist Planning of Clinical Trial
- Start-up Meeting Checklist
- Start-up Meeting Agenda

## 9 DEFINITIONS

SOP Definitions.

| Abbreviation | Term |
|---|---|
| ASR | Annual Safety Report |
| CRO | Contract Research Organisation |
| CTIS | Clinical Trial Information System |
| EC | Ethics Committee |

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|---|---|
| EEA | European economic area |
| EMA | European Medicines Agency |
| GCP | Good Clinical Practice |
| GMO | Gene Modified Organism |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| MA | Marketing Authorisation |
| MS | Member state |
| NoMA | Norwegian Medicines Agency, Statens legemiddelverk |
| IMPD | Investigational Medicinal Product Dossier |
| Q & A | Question and Answer |
| REK | Regional komité for medisinsk og helsefaglig forskningsetikk |
| RFI | Request for information from authorities to sponsors in CTIS |
| RMS | Reporting member state |
| SOP | Standard Operating Procedure |

## 10 CHANGES SINCE LAST VERSION

CT SOP version no 1.4

Main changes from version 1.3: updated with need for registration of trials in clinicaltrials.gov and detailing more for CTIS applications.