1 PURPOSE

To define how First In Human (FIH) and early phase studies shall be planned and conducted at Norwegian Early Phase Clinical Trials Units (EPCTUs) irrespective of whether the sponsor is commercial or not.

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

The purpose of FIH trials is to evaluate an Investigational Medicinal Product (IMP) in humans for the first time, to study the human pharmacology, tolerability and safety of the IMP and to compare how effects seen in non-clinical studies translate into humans.

2 SCOPE

Particular care is necessary when a new drug is given without previous testing on humans. Therefore FIH studies, like all early-phase clinical trials, should take place in appropriate clinical facilities and be conducted by investigators and medical staff with appropriate levels of training and experience of early phase clinical trials (EPCTs). They should also understand specific characteristics of the IMP, its target and mode of action. The training must include relevant medical expertise and GCP training. All university hospitals in Norway should be able to fulfil the requirements for conducting EPCTs, while FIH studies will need special attention in specific units. Preferably, these units should have passed an audit or an inspection.

Risk mitigation is a core element in EPCTs, and is pivotal in FIH studies. Risk identification and analysis is based on documents such as the study protocol and Investigator's Brochure (IB) and must identify risk factors for the specific study. These may be, but are not limited to, logistics, facilities, equipment, study population, study staffing, IMP, the possible need for an additional emergency medicine unit, dosing (especially at dose escalation) and emergency routines. Specific populations, such as pediatric patients and patients with cancer or rare diseases, may need special attention. The risk analysis should be performed early in the planning phase of the study and always well before the study starts and should involve both the sponsor and the EPCTU.

This SOP will, together with the Relevant Documents listed below, describe the particular requirements for quality systems and how FIH studies/EPCTs should be planned and conducted (operation of the unit) in compliance with relevant international and national regulations, at all Norwegian EPCTUs. Supplementary SOPs adhering to clinical drug trial conduct of all phases will also apply to EPCTs, and are listed at the NorCRIN homepage.

If the sponsor is external to the institution, e.g. a pharmaceutical company, the sponsor's SOPs can be used, provided they are in line with national and international laws, regulations and ICH GCP.

3 RESPONSIBILITIES

List of roles: Sponsor, EPCTU Manager, Principal Investigator, Co-Investigator, Site Project Manager / Study Nurses

3.1 Sponsor

Sponsor is responsible for writing the protocol according to the standards for FIH-studies/EPCTs and implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials. This includes doing a risk assessment for the totality of the trial.

3.2 EPCTU Manager

Ensure that the study team is appropriately qualified, experienced and trained for conduction of FIH studies/EPCTs and handling of emergency situations. See to that education/training is up to date, such as annual life support training - CPR (Cardiopulmonary resuscitation; S-CPR for nurses and A-CPR for physicians). A documented list of life support training must be kept at the EPCTU.

Moreover, the EPCTU Manager shall:

1. Secure that the unit is appropriately staffed at any time of study conduct
2. Take responsibility for facilities and basic structure of the unit.
3. See to that fire evacuation procedures are established.
4. See to that back-up power supply is available.
5. Take responsibility for the security of the facility with respect to unauthorized or limited access.
6. See to that provisions are in place for insurance and indemnity.

3.3 Principal Investigator (PI)

In addition to the comprehensive requirements pertaining to being a PI, additional and more specific requirements for PI in FIH studies/EPCTs comprise:

1. Being thoroughly familiar with the European Medicines Agency, EMA, Guideline on strategies to identify and mitigate risks for FIH and ECTs with IMPs.
2. Having relevant knowledge in pharmacology to secure an appropriate review of pre-clinical data, assess the pharmacology and subsequent aspects, such as the proposed starting dose, dose escalation proposal/stopping criteria etc for IMP. For FIH in particular, consulting clinical pharmacology expertise may be advisable.
3. Obtaining sufficient information and knowledge regarding the study procedures and IMPs (such as targets, mechanism of action and potential adverse events) to be able to assess the risk for possible harm, perform Informed Consent process and make clinical judgments during the study.
4. Performing a risk analysis based on the protocol and the IB, for each study, together with the study team. The risk evaluation should have a quality at least comparable to SOP Quality and Risk Management and clearly conclude that anticipated risks and risk mitigation are adequately balanced (See section 4.1.2 for details).
5. Creating/reviewing the application for the Ethics Committee (EC) and Informed Consent documents (ICD), so that they cover specifically important information regarding drug characteristics (pharmacological and toxicological) to support start and maximum dose and explain and justify risks for the specific study.
6. When relevant, seeing to that the ICU is informed about the specific study before study start and dosing of patients.
7. Supervising dosing procedures on site during and after dosing. This could also be delegated to a Co-Investigator.

8. Being aware of and follow the specific stopping rules for the study.

9. Writing drug requisitions for the study.

10. Nominating a co-investigator

3.4 Co-Investigator

The Co-Investigator should perform the study specific tasks that have been delegated by the PI.

3.5 Site Project Manager / Study Nurses

Site Project Manager and/or Study Nurse shall see to that such as vital function monitoring devices are operative, including control of alarms, and emergency equipment, emergency cart, emergency medication and temperature control for IMPs is performed before study start. Moreover, she/he shall:

1. Set up and maintain the Trial Master File (TMF) or Investigator Site File (ISF) as applicable.

2. For each study suject, follow the study flow chart.

3. Prepare IMP if this is not done by the pharmacy. Only simple processes of dissolving/dispersing or diluting/mixing of IMPs should be made by the study staff. More complicated processes of dissolving/dispersing or diluting/mixing must be made by units with adequate facilities, knowledge and qualifications, e.g. a pharmacy.

4. Connect study subjects to appropriate vital sign monitoring.

5. Administer lifesaving adrenalin, when needed.

4 PROCEDURE

4.1 Procedures before study start

4.1.1 Qualified staff

It is important that the unit has trained and experienced staff available to undertake the trials they are conducting. Minimum staffing during the dosing phase must be two study nurses and medical supervision of PI or co-investigator during and after dosing. Time frames for the dosing phase will be set depending on the specific study.

4.1.2 Risk analysis

When performing the risk assessement, the FIH/EPCTU shall ensure that all relevant safety aspects of the trial are considered. The sponsor's risk evaluation should be reviewed. The FIH/EPCTU shall make their own assessment and retain any discussions with the sponsor (whether sponsor is a hospital or pharmaceutical/biotechnology company). Upon a possible disagreement with the sponsor; the PI should seek review by a professional with relevant expertise at the hospital.

Special considerations should be brought to:

1. Confirmation/re-calculation of the starting dose and dose increments. In order to determine a safe starting dose, the methods used for determination of the strength and/or the potency of the product need to be relevant for the intended mechanism of action, reliable and qualified.

2. Any dose escalation procedures.

3. Relevance of study design (i.e. population, administration, assessments etc.).

4. IMP (i.e. relevance of safety/toxicology information, mode of action, the nature of the target, pharmacokinetic (PK) and pharmacodynamic (PD) information, a description of potential polymorphisms etc.).

5. Any specific rescue medications/antidotes, supportive emergency facilities and staff, specific emergency scenarios etc.

6. Extra staffing/resources (i.e. identifying specific training, expertise, facilities or specific location/wards in unit for conduct of certain trials etc.)

A written document in which identified risks and risk mitigation measures are adequately balanced should always be available.

4.1.3 Pre-study clinic meeting

A follow up of the risk analysis and actions performed will be done by the PI and study team at a pre-study clinic meeting.

4.1.4 Dry run

A study rehearsal, "dry run procedure", will be performed before the study starts. During this rehearsal, all members of the study team will be present. A flow chart with all the procedures for the specific study will be set up and reviewed step-by step from the time point when the study subject enters the EPCTU until her/his study treatment is completed.

4.1.5 Intensive Care Unit (ICU)

The EPCTUs must have immediate access to equipment and staff for resuscitating and stabilizing individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of Intensive Care Unit facilities (ICU). Procedures must be established between the EPCTU and its nearby ICU regarding the responsibilities and undertakings by each unit in the handling and care of patients.

The PI or designee will inform the ICU about the specific study before study start. Documentation regarding the given information shall be kept in the Investigator's Site File.

It is recommended that a general agreement is in place between the departments involved, well before start of the study.

4.1.6 Checklist before study start

The Site Project Manager or Study Nurse will review the checklist under section 3.5 so that all tasks/items are performed or checked, such as temperature control for IMP, emergency chart check, alarms etc.

4.2 Procedures during study conduct

4.2.1 PI

The PI shall supervise dosing procedures on site during and after dosing. This can also be delegated to a Co-Investigator.

4.2.2 IMP and dosing

A temperature control of the refrigerator/room where the IMP is stored will be performed before any IMP is given to any study subjects. Preferably a pharmacy will handle this up to the time of administration.

Before dispensing the IMP to a subject the staff will verify the subject's identity to ensure that IMP is dispensed/administered to the correct individual. IMP will be dispensed/administered in accordance with the protocol and/or any other study specific requirements.

Before the IMP is dispensed/administered to the subject a second member of the study team will check that the correct quantity/batch/dose etc., has been prepared and that the IMP is administered to the right subject. This will be documented on the IMP source documents for the specific study.

When relevant, dose increases will proceed with caution and there must be an adequate period of observation between the administration of the IMP to the first, second and subsequent subjects in a cohort to observe and interpret reactions and adverse events. The duration of the interval of observation must be justified and will depend on the properties of the product and the data available, including non-clinical PK and PD.

Administration in the next dose cohort must not occur before participants in the previous dose cohort have been treated and data/results from those participants are reviewed in accordance with the protocol. The decision to proceed to the next cohort will be discussed with sponsor when relevant, and should be documented.

4.2.3 Study population

The study team must ensure that study subjects are correctly identified and that their medical history is thrustworthy (checked with their primary doctor, "fastlege"). The financial compensation to study subjects entering a trial must be reasonable and is not expected to match a day's salary at work. It should be approved by the Ethics Committee.

The study protocol will define the inclusion/exclusion criteria for the study.

4.2.4 Monitoring of adverse events/reactions

The trial protocol shall provide a specific plan for monitoring of adverse events or adverse reactions. The mode of action of the IMP, findings in the non-clinical toxicity studies and, particularly for FIH, any anticipated responses will be used to identify likely adverse events. Minimum safety and tolerability measurements shall comprise physical examination, cardiac-pulmonarymonitoring including vital signs, clinical laboratory parameters at pre-dose and relevant post-dose time points. The data should be compared with screening data.

All clinical staff must be trained to identify adverse reactions and how to respond to those or any other adverse events. A rationale for the length of the monitoring period and the nature of monitoring within, and if deemed appropriate outside, the EPCTU must be provided in the protocol.

Participation in the specific trial must for each study subject be recorded in the medical journal (and in the subject's "kjernejournal", in which it is to be deleted after the study follow up period). In addition, they must all be provided with a contact telephone number to call if there should be questions related to their study participation.

The protocol or referenced document should include a plan for prompt communication of serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), between trial subjects, staff and the sponsor.

In the case of emerging safety issues, i.e. an SAE, the investigators must inform the sponsor and participants as soon as possible, and at least prior to any planned next dosing.

4.2.5 Stopping rules

The protocol must define stopping rules for the cohort and study such as processes and responsibilities for making decisions about dosing of subjects, dose escalation and stopping the cohort or study.

4.3 Procedures after study completion

The general study procedures in NorCRIN for close-out must be followed.

5 NON-CONFORMANCE MANAGEMENT

All non-compliance should be handled according to the procedures for handling non-compliance of the individual health facility or institution.

6 REFERENCES

6.1 External References

- Guideline on strategies to identify and mitigate risks for first in human and early clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 Rev. 1
- Guidance for the conduct of Good Clinical Practice inspections, Phase I units. ENTR/F/2/SFD(2008) 34961
- Guidelines for Phase I clinical trials, 2018 edition, The Association of the British Pharmaceutical Industry (ABPI).
- ICH Guideline for Good Clinical Practice E6 (R2)
- Forskrift om klinisk utprøving av legemidler til mennesker FOR-2009-10-30-1321

6.2 INTERNAL REFERENCES

- SOP Opplæringsplan og kompetansekrav (including Delegation Log, Training Log)
- SOP Quality and Risk Management
- SOP Clinical Trials of AdvancedTtherapy Medicinal Products
- SOP Rapportering av uønskede medisinske hendelser og bivirkninger
- SOP Avslutning og arkivering av kliniske legemiddelutprøvninger
- SOP Referansedokument

7 ATTACHMENTS

- Mal risikovurdering

8 DEFINITIONS

- Definisjoner

9 CHANGES SINCE LAST VERSION

New document.

List of abbreviations

AE	Adverse Event
CPR	Cardiopulmonary Resuscitation
EC	Ethics Committee
EMA	European Medicines Agency
EPCT	Early Phase Clinical Trial
EPCTU	Early Phase Clinical Trial Unit
FIH	First in Human
IB	Investigator's Brochure
ICD	Informed Consent Document
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File