# WP7 NorCRIN:
# Proposal for requirements
# at
# Early Phase
# Clinical Trials Units
# in Norway

**The composition of the working group WP7:**

Hasse K. Zaré, Oslo universitetssykehus (OUS)

Ola Dale, St Olavs Hospital (St Olav)

Steinar Aamdal (OUS)

Kristin Øwre (OUS)

Paal Fr. Brunsvig (OUS)

Bjørn Tore Gjertsen, Haukeland universitetssykehus (HUS)

Anne-Sofie Sand, Universitetssykehuset Nord-Norge (UNN)

Anne Hansen Ree, Akershus universitetssykehus (AHUS)

Tove Buhl, Stavanger universitetssykehus (SUS)

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# Background

There has been a dramatic decline in the number of clinical trials on pharmaceutical products in Norway and elsewhere in Europe in the 2000s. In 2003, approximately 16,000 patients were involved in industry-financed drug trials; compared to 6,700 in 2013. Also the number of academic clinical drug trials have been reduced in this period, although less dramatic than for the industry sponsored trials. The Nordic Co-operation Committee for Medicine published a report on the status and future opportunities for health research in the Nordic countries in 2011. It was concluded that clinical research needs more attention. Clinical research and patient-adapted medicine are given significant weight in the European Health Program Horizon 2020. To facilitate and secure high quality in clinical trials in the specialist health services, a national infrastructure network NorCRIN (http://www.norcrin.no/) was established in 2012. This network is a part of the European Research Infrastructure Cooperation, ECRIN (http://www.ecrin.org/). Also the Nordic Trial Alliance (http://nta.nordforsk.org/) was established to promote Nordic clinical trial cooperation.

According to *Legemiddelmeldingen (Meld. St.28)* (The Norwegian Government report on medicinal drugs: https://www.regjeringen.no/no/dokumenter/meld.-st.-28-20142015/id2412810/), Early Phase Clinical Trials (EPCT), testing of new, costly medical technology, and the use of genetic and biological data will require centralization, as well as infrastructure and competence building at university hospitals. Early Phase Clinical Trials Units (EPCTU) will help to transfer knowledge and investments in medical basic research to practical clinical medicine, thereby developing new diagnostics and treatment for the benefit of patients. *There is a need to strengthen the capacity of Early Phase Clinical Trials Units in Norway.*

EPTCU are specialized units (facilities) for interventions in patients and volunteers aiming at mitigating risks and secure quality in Early Phase Clinical Trials. Phase I comprises high-risk trials with first-in-human (FIH) compounds, biologicals, and some vaccines, as well as other trials that carry significant uncertainties regarding subject safety. Early Phase Clinical Trials also comprises low-risk pharmacokinetic trials of new drug formulations, administration schedules, or combinations of well-known.

The common concept of drug approvals based on a consecutive chain of trials from Phase I - III is under change. Recently, the drug pembrolizumab was approved by the U.S. Food & Drug Administration on the basis of a large Phase I trial only (N=1,235 patients). Such trials most likely require access to EPCTU.

*It follows that requirements for Early Phase Clinical Trials Units must be dynamic and give high priority to procedures, quality systems, competence and capacity of the EPCTU staff.*

# Scope

WP7 prepared a report termed “Mapping of Early Phase Clinical Trials Units in Norway” which was sent to NorCRIN on the 17th of January 2017. The second task for WP7 is to build up *a comprehensive list of proposal for requirements for EPCTU in Norway***.** The purpose is to recommend specific requirements to EPCTU harmonized with available international and European documents containing guidance on EPCT. This list should assure that EPCTU not only meet, but also surpass the basic regulatory Good Clinical Practice (GCP) aspects, by having additional “best practice” procedures that encompass the highest standards for avoiding harm to trial subjects and for handling medical emergencies, in addition to assuring sponsors that EPCTU make significant contributions to enhance safety issues of EPCT. Quality in all aspects of study conductance should also be secured.

The ultimate goals are:

1. To minimize potential risk to study participants who take part in EPCT.

2. To conduct EPCT, in all its aspects, formal as scientific, at a high level of international standard.

*It is mandatory that EPCTUs demonstrate that they can conduct EPCT, for some also capacity to conduct high-risk studies with FIH (first in human)/ first-time-in-patient (FTIP) compounds.*

The recommendations are based on the following documents:

- International council for harmonization of technical requirements for pharmaceuticals for human use (ICH), Harmonized guideline, Integrated addendum to ICH E6 (R1): Guideline for good clinical practice E6(R2)
- Concept paper on the revision of the ‘Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products’ (DRAFT)(EMEA/CHMP/SWP/28367/07)
- 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)
- MHRA (Medicines and Healthcare products Regulatory Agency), UK, Phase I, Accreditation Scheme, Requirements
- NEXT (National Experimental Therapy Partnership), DK
- Standard Operating Procedure, First In Human (FIH) studies, Karolinska Trial Alliance – KTA Phase I unit

# Requirements of an Early Phase Clinical Trials Unit

*WP7 would recommend that an EPCTU profile should contain:*

- Personnel with high professional level and relevant research profiles
- Experience with national cooperation in EPCT.
- National process for feasibility-inquiries between different professional organizations and center participants.
- Principal Investigators (PI) should be recognized within their disciplines/fields.
- Response time of <48 hours for relevant communication.
- A relevant set of standard operating procedures (SOPs)

For FTIP it should also be required:

- Advanced experience, competences, and professional collaboration with EPCT
- PI should have significant experience with EPCT
- The ECPTU should provide study specific documentation of risk mitigation in general and of individual trials
- Pre-approval of the EPCTU by the Norwegian Medicines Agency (NOMA), pending establishment of a pre-approval system

# Operation of the Accreditation or pre-approval scheme

There is no accreditation system for EPCTU in any of the Scandinavian countries. In Sweden a unit can apply for pre-approved verification for FIH trials. The Swedish Medicines Agency then performs an inspection of internal procedures for safety and care, premises and personnel. If approved, the unit is pre-approved for FIH trials for 3 years, provided there are no major changes in personnel or premises. In United Kingdom, units can apply for accreditation. The inspections conducted for the accreditation scheme encompass a wider scope than standard GCP inspections and include a detailed review of the unit's systems and procedures relevant to the requirements. Once an inspection has demonstrated that the requirements of the scheme are met, the unit will be accredited.

# Accreditation or pre-approval of EPCTU in Norway

An EPCTU must demonstrate that it is able to carry out clinical trials with compounds at actual levels of risk, for some also high risk-procedures. This means they must have formal procedures in place/be familiar with the national procedures posted at NorCRIN homepage (www.norcrin.no) and hold appropriately trained and experienced staff available to cover all requirements. It should be possible for the

EPCTU to apply for pre-approval. This is especially important for those that have never been tested in human (FIH) and those that require review of risk factors. The NOMA, which may serve as the relevant National Competent Authority, should be able to assess, inspect, and verify that all of the requirements are met (see below).

We believe that it should be possible for the NOMA, in a same manner as in Sweden, to pre-approve relevant units in Norway. The certificate should be valid for up to 3 years, with re-inspection performed prior to renewal of the certificate. Units are required to submit to the NOMA any significant changes or variations over this 3-year period. If changes at the unit result in any of the verification criteria no longer being met, then the NOMA must be informed immediately and may suspend the verification.

NOMA reports any information on the verification or suspension/termination of the unit status to REC (Regional Ethical Committee) in order to assist the REC with their responsibility to carry out site-specific assessments of the unit.

## *WP7 will suggest that EPCTU have at least the following recommendations:*

| **Type** | **Required** | **Advantageous** |
|---|---|---|
| Industry and academic cooperation | • Experienced with EPCT<br>• Documentation that any critical findings from Audit/Inspections during the last 5 years/last 10 trials have been adequately followed up | • >10 clinical trials last 5 yrs<br>• Experience with marketing in patient recruitment<br>• Experience as a National Coordinator |
| Cooperation | • Active and interested in national and international cooperation | |
| Quality system/Standard Operating Procedures (SOPs) | • Written SOPs for every aspect of the unit's activities including all the accreditation requirements.<br>• Procedures for handling common medical emergencies (Hospital SOP and agreement with emergency dep.)<br>• Out-of-hours medical cover and contact with sponsor or IMP responsible person(s)<br>• Continuous training, including competency assessments for all key activities, and emergency resuscitation procedures<br>• Subject recruitment, including identification, medical history<br>• Staffing level/resourcing<br>• Equipment maintenance system | • Patient databases which can be used for patient recruitments<br>• Admission to registry which can be used as a recruitment base |
| Capacity<br>Unit facilities & procedures | • Defined as EPCTU<br>• Sufficient space for conducting EPCT, including facilities for monitoring<br>• Access to relevant equipment and personnel in relation to laboratory, pharmacy, radiology (CT and MRI scan).<br>• Cooperation agreements with relevant departments including documentation that medical equipment is calibrated and validated.<br>• Access to medical emergencies and facilities | |
| Key personnel, Background and qualifications | • GCP training and updated CV < 2 years old for all study personnel<br>• Expectation for minimum qualifications, training and experience for key roles and responsibilities<br>• Experienced in eCRF<br>• Trained to handle medical emergencies<br>• Competent to perform risk assessment and mitigation | • > 2 PIs, > 2 study nurses |
| Communication | • Investigator and study nurses can provide <48 hours response upon requests<br>• Clearly defined who is the Investigator and study nurse primary contact<br>• Back Up personnel for key persons in the department in relation to follow timeline for reporting to industry /others) | • Feasibility response time <5 days (or according to agreement)<br>• Queries response time <5 days (or according to agreement |

# Summary

The WP7 has made a list of proposals for requirements of Early Phase Clinical Trials Units (EPCTU) in Norway. It has been important for WP7 to keep a balance by not making too strict requirements that may exclude most EPCTU from running EPCT, however, risk and competence must be aligned. At the same time, there is a need of certain requirements for infrastructure and competence/capacity for units to secure quality in study execution and safety for the subjects in harmony with international recommendations. The key issue is that an EPTCU can document that it is capable of handling the assignments it may undertake.

The next step would be to determine what is adequate documentation and develop standard procedures for the EPCTUs. Some of the EPCTU in Norway will already have documentation which can be built on. Others must be developed. This will pave the way to have a list of national standard procedures for EPCTU in Norway.

The working group furthermore recommends that NorCRIN enters into a dialogue with the Norwegian Medicine Agency (NOMA) about quality control of EPCTU. The collaboration with NOMA will brings us closer to the system that already exists in Sweden, i.e. preapproved units.

## Definitions

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|---|---|
| Phase I (according to Statutory Instrument) | A clinical trial to study the pharmacology of an investigational medical product (IMP) when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial.<br>Note: It is recognized that this definition is too restrictive to apply to all Phase I trials, for example, in oncology, anesthesia, genetic disorders, immunological. |
| Early Phase | All types of Phase I trials using either healthy volunteers, volunteer patients and/or patients, including FIH, FTIP. |
| First in human (FIH) | IMP is administered to a human for the first time. |
| First time in patient (FTIP) | This is a subset of FIH, where it would be unethical or not possible to administer the IMP to a healthy volunteer. Therefore, the IMP is administered to a patient. It does not refer to a Phase II trial where the IMP was previously given to a healthy volunteer. |
| Healthy volunteer (HV) | A well (generally healthy, not sick) person who agrees to participate in a clinical trial for reason other than medical purposes and receives no direct health benefit from participating. |
| Patient volunteer (PV) | A person who has a specific medical condition (e.g. asthma or diabetes etc.) relevant to the clinical trial that agrees to participate in a clinical trial for reason other than medical purposes and is unlikely to receive a direct health benefit from participating.<br>[Usually recruited via advertising or units may hold a panel of volunteers.] |
| Patient | A person being treated for a specific medical condition, who has been invited or referred by the GP/consultant to participate in a clinical trial. Patients may receive a therapeutic benefit from the trial. |