Ahus - Roles and responsibilities in clinical trials of pharmaceuticals

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1. Purpose

The purpose of this procedure (Standard Operating Procedure - SOP) is to describe the overall division of roles, responsibilities and tasks in the planning, start-up, implementation and termination of clinical drug trials.

The SOP shall ensure compliance with national and international laws, regulations and the International Council for the Harmonisation of technical requirements for for pharmaceuticals for human use - Guideline for Good Clinical Practice (ICH GCP) specified in the Reference Document for clinical trials.

Until January 31, 2025, two pieces of legislation will be in effect; the old legislation "EU Directive 2001/20/EC (of the European Parliament and of the Council of 4 April 2001)", and the new legislation "EU Regulation 536/2014 (of the European Parliament and of the Council of 16 April 2014)". The current legislation for each study depends on which legislation was used when the authorities applied for approval of the study, and whether the study has been transferred to the new legislation or not.

2. Scope

The SOP is applicable to clinical drug trials at Akershus University Hospital HF (Ahus) and supplements the document "Responsibility in Quality and Research Projects," EQS ID 15673.

If the sponsor is external, for example, a pharmaceutical company, the sponsor's SOPs may be used, provided they are in line with national and international laws, regulations, and guidelines.

3. Job Description

3.1. Responsibility

The responsibilities and tasks for clinical studies are derived from:

- ICH GCP R2
- Regulation on Clinical Trials of Medicinal Products for Human Use and guidances ("old legislation," valid during a transitional period until 31 January 2025)
- Health Research Act with associated legislation
- EU Regulation 536/2014 ("new legislation" – from 31 January 2022 for studies applied through the new portal Clinical Trials Information System (CTIS))

The sponsor has overall responsibility for conducting drug trials in accordance with applicable laws, regulations, and guidelines. The sponsor's responsibilities are described under point 4.1 in this SOP.

The sponsor may transfer certain or all of its study-related tasks and functions to a third party, such as a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the study data will always rest with the sponsor.

The sponsor should have an overview of study-related tasks and functions performed on their behalf. The transfer of tasks should be specified in a written agreement.

The principal investigator at each study site is responsible for conducting drug trials in accordance with the current study protocol, laws, regulations, and guidelines.

Tasks can be delegated. See point 8.1, table 1, for delegation of sponsor tasks..

4. Roles, Responsibilities, Authorities, and Task Allocation

The primary functions/roles in the execution of clinical drug trials encompass the sponsor (healthcare institution, research lead), coordinating investigator/principal investigator for single-site studies/national coordinating investigator for multi-site studies, principal investigators, study personnel, and monitors. A brief description of these functions, roles, responsibilities, and tasks is provided below.

Coordinating investigators/principal investigators for single-site studies and national coordinating investigators for multi-site studies bear the same responsibilities and are synonymous terms in this document. The term "coordinating investigator" will be employed henceforth.

Current NorCRIN procedures tailored for use in clinical drug trials, as well as flowcharts for the utilization of these procedures, are accessible on the NorCRIN website. During the transitional period of 3 years for the implementation of the new regulation (EU Regulation 536/2014) for clinical trials, two sets of NorCRIN procedures will be available; LM procedures ("old legislation") and CT procedures (new regulation 536/2014).

A distinction is made between single-site and multi-site studies. A single-site study refers to a trial conducted at a single institution. Conversely, a multi-site study denotes a trial conducted, using the same protocol, across multiple institutions.

4.1. Sponsor

In investigator-initiated studies, as a general rule, the healthcare institution/institution where the principal investigator (single-site study) or national coordinating investigator (multi-site study) primarily operates will serve as the sponsor.

In clinical drug trials in Norway conducted in collaboration with colleges and universities, an agreement may be established to define the Sponsor role.

For clinical drug trials commissioned by the industry or other non-profit organizations in Norway or abroad, the principal funder will typically assume the role of the sponsor.

In the new regulation, there can be more than one sponsor. Co-sponsors should be subject to the same sponsorship responsibilities. However, it is possible to distribute sponsorship through a written agreement

At Ahus, the sponsor will be represented by the Head of Department. In cases where the head of department is the national coordinating investigator or principal investigator, sponsorship responsibility will be represented at the next level in the management line. When signing general agreements/contracts, the Power of Attorney booklet applies to Ahus Ahus - Powers of attorney at Akershus University Hospital, cf. "The Research Area".

Below is an account of the sponsor's responsibilities and tasks. With regard to delegation of sponsorship tasks, reference is made to Section 8.1, Table 1.

4.1.1 Responsibilities and duties

The sponsor's responsibilities and tasks for drug trials are set out in ICH GCP chapter 5, the regulations on clinical trials of medicinal products for human use and sections 5 and 6 of the Health Research Act with regulations.

Tasks may be delegated to a greater extent than described in this procedure, for example in international clinical trials where the sponsor is not a Norwegian institution and tasks for practical reasons should be performed nationally. These delegations must be regulated in a written agreement between the parties.

Of the tasks that it is the responsibility of the sponsor to ensure are followed up, reference is made to section 8.1, Table 1.

4.2. Coordinating investigator

For clinical trials, the coordinating investigator is responsible for overseeing the coordination of all investigators across various study sites. In addition to ensuring that investigators fulfill their responsibilities and tasks, the coordinating investigator is also tasked with carrying out sponsor duties in other countries in international studies, in addition to their own country.

4.2.1 Responsibilities and Tasks

The coordinating investigator can delegate sponsor tasks to principal investigators, Clinical Trial Units (CTU), or others in different countries through a written agreement. The responsibility for these tasks will remain with the coordinating investigator.

4.3. National Coordinating Investigator (applies only to studies following the old directive)

According to the outgoing directive, the national coordinator is the responsible individual towards the ethics committee (REK in Norway). This role is not outlined in the new regulation (EU Regulation 536/2014).

The national coordinating investigator serves as a liaison between the sponsor and the Norwegian centres. The national coordinating investigator can also act as the principal investigator in their own institution and will then assume the same responsibilities as described in point 4.5.

Responsibilities and Tasks

The responsibilities and tasks of the national coordinating investigator are detailed in section 8.1, table 1, and align with ICH GCP Chapter 4, the Regulation on Clinical Trials of Medicinal Products for Human Use, and the Health Research Act §5, to the extent that they are applicable to clinical drug trials.

4.4. Medical monitor

The sponsor should have an individual or a defined group with the authority to assess safety aspects of a clinical drug trial. This includes assessing serious adverse events (SAEs), reporting suspected unexpected serious adverse reactions (SUSAR) to relevant authorities, preparing an annual safety report, informing investigators about SUSARs and any changes to the risk assessment of the study. It is recommended to have a group of people as the medical monitor, but the monitor can also be the same person as the national coordinating investigator. In blinded studies, medical monitors should be able to see unblinded data when needed.

4.5. Principal investigator

The principal investigator is an investigator who leads the trial at the individual test site (HF or other institution). As the principal investigator, it must be possible to document that the person in question possesses sufficient qualifications to be able to lead and carry out the trial in his/her own HF/institution, including documenting ICH GCP knowledge. The Regulations relating to clinical trials of medicinal products for human use require the principal investigator to be a doctor or dentist.

4.5.1 Responsibilities and duties

The principal investigator's responsibilities and tasks in drug trials are set out in ICH GCP chapter 4 and in the Regulations relating to clinical trials of medicinal products for human use and Section 5 of the Health Research Regulations to the extent appropriate. Of the tasks assigned to the principal investigator, reference is made to Section 8.1, Table 1.

In clinical trials conducted in a single centre (single-centre study), the tasks of the principal investigator will also include the tasks of the national coordinating investigator (see section 4.3, as well as section 8.1, table 1).

4.6. Student co-worker

The principal investigator can delegate tasks to named student employees. Such delegation must be in writing (SOP Cooperation agreements, information routines and delegation of tasks). Study staff will normally be other investigators, and study personnel from the same institution contributing to the project.

When delegating, the principal investigator has a special responsibility to ensure that the study staff possess sufficient competence to carry out the assigned tasks. Only specifically defined tasks can be delegated, not responsibility.

4.6.1 Responsibilities and duties

Study personnel carry out tasks as delegated by the principal investigator. These tasks should be specified in a delegation log or a similar document.

Study personnel defined as healthcare professionals under the Health Personnel Act, however, bear independent responsibility according to § 4 concerning the requirement for appropriate patient care.

4.7. Monitor

Every drug trial must appoint an individual (monitor) responsible for monitoring the study. The monitor operates on behalf of the sponsor. The monitor can be either internal or external but cannot be the same person as any of the investigators or study personnel.

The monitor is expected, among other things, to have comprehensive knowledge of all relevant laws and regulations pertaining to the trial and adequate scientific and/or clinical knowledge about the studies.

4.7.1 Responsibilities and Tasks

The monitor is to conduct monitoring in accordance with the current monitoring plan/agreement for the individual trial and in line with ICH GCP 5.18, including conducting monitoring visits and reporting to the sponsor/principal investigator through monitoring reports, as per the SOP Monitorering.

5. Handling of Deviations

Handling of deviations concerning this SOP is done according to the procedures for handling deviations of each healthcare institution or individual institution. Deviations identified during the monitoring of a clinical trial should be managed in accordance with the SOP Protocol deviation handling.

6. Bakground Information

6.1. External Background Documents

- Health Research Act – particularly §§ 5 og 6
- Health Personnel Act – particularly § 4
- Regulation on Clinical Trials of Medicinal Products for Human Use 2009-10-30-1321
- Regulation on the Organization of Medical and Health Research 2009-07-01-955 – particularly §§ 3, 4, 5 og 6.
- EU Regulation 536/2014 on clinical trials
- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) - particularly chapter 4 og 5
- Guidance for the regulation of 30 October 2009 on clinical trials of medicinal products for human use
- Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)
- General Data Protection Regulation, EUs personvernforordning
- Act on the Processing of Personal Data

6.2. NorCRIN background documents

- SOP Collaboration agreements, information procedures, and task delegation
- SOP Application process, approvals, and initiation
- SOP Case Report Form (CRF) and Patient Reported Outcome (PRO) form management
- SOP Randomisation, blinding, and unblinding
- SOP Reporting of adverse medical events and side effects
- SOP Drug management at the start of clinical trials
- SOP Drug management during the execution of clinical trials
- SOP Drug management at the conclusion of clinical trials
- SOP Training plan and competency requirements
- SOP Study Files

- SOP Conclusion and archiving of clinical drug trials
- SOP Monitoring
- SOP Clinical trials of advanced therapy medicinal products
- SOP Quality and Risk Management
- SOP Protocol deviation handling

6.3. Internal Background Documents

EQS ID	Dokument
32438	Clinical drug trials (reference document, NorCRIN)
15673	Responsibilities in quality and research projects
33743	Storage, archiving, and deletion of health and personal data
34153	Treatment, closure, and follow-up of research-related adverse events/deviations
34152	Workflow – handling of research-related adverse events/deviations
8238	Authorities at Akershus University Hospital
32429	Archiving of documents for quality and research projects in Public 360
32435	Remote storage of questionnaires/research data (Skytta

7. Definitions

- NorCRIN- definitions ” old regulations”
- NorCRIN-definitions ” new regulations”

Abbreviation	Term
CTIS	Clinical Trial Information System
DPIA	Data Protection Impact Assessment
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

8. Attachment

8.1. Table 1

Responsibilities and Tasks for Sponsor, National Coordinating Investigator, and Principal Investigator

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
	A = Accountability D = Delegated Task			
General Responsibilities	Ensure adherence to GCP (Good Clinical Practice).	A	D	A
	Facilitate the procurement of essential insurance for trial participants.	A	D	
	Ensure the validity of insurance across all implicated nations.	A	D	
	For advanced therapeutic medicinal product studies (such as somatic cell therapy, gene therapy, or tissue therapy): ensure that specific requirements for the protocol and informed consent are included in accordance with the SOP Clinical Trials of Advanced Therapy Medicinal Products	A	D	
	Ensure that the trial is conducted in accordance with the approved protocol.	A	D	A
	Maintain an overview of study-related tasks and functions performed on behalf of the Sponsor.	A	D	
	Facilitate monitoring, and if applicable, audits and inspections.	A	D	A

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Internal Anchoring (and Funding)	Ensure sufficient anchoring of the trial within one's own healthcare institution upon registration via eForm (data protection officer).		A	A
	Gather relevant information about the storage and		A	A

	processing of personal data, and ensure that a data protection impact assessment (DPIA) is conducted if necessary, and that the legal basis for handling personal and health data is in place.			
	Ensure proper handling of human biological material and appoint a responsible person for the research biobank.	A	D	D
	Ensure that the institution where the principal investigator is employed has systems and procedures in place to ensure that research data is processed and stored in accordance with internal procedures, EQS IDs 33743, 32429, and 32435.			A
	Register the study on Ahus.no, and clinicaltrials.gov if applicable. EQS ID 34316	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Application to the Authorities *Old Legislation*	Ensure that approval for the study has been obtained from REK and the Norwegian Medicines Agency before the start of the study. Ensure that all participating study centres are registered in the applications.		A	
	Ensure that study approval is available for other participating countries.	A	D	
	Obtain approvals for significant amendments from REK.		A	
	Obtain approval for significant amendments	A	D	

	from the Norwegian Medicines Agency and other relevant authorities if applicable.			
	Ensure that approvals for application-required amendments in other participating countries have been obtained.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Application to the Authorities *New Legislation*	Obtain approval for the study from the authorities and REK via the EU portal CTIS. Ensure that all participating centres in all participating countries are registered in the application.	A	D	
	Ensure that the study has approvals from relevant authorities for other participating countries, if they are not included in CTIS (outside the EEA).	A	D	
	Obtain approvals for significant amendments from authorities and ethics committees through CTIS.	A	D	
	Ensure that significant amendments are approved by relevant authorities for other participating countries, if they are not included in CTIS (outside the EEA).	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Protocol, Information, Consent, IB/SmPC	Draft the study protocol, information leaflet, consent form, and if applicable, Investigator's Brochure and/or pharmaceutical-	A	D	

	chemical documentation, CRF/questionnaire, as well as study-specific guidelines.			

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Contracts and Agreements	Ensure that the trial is monitored.	A	D	
	Enter into a written agreement with collaborating institutions and others.	A	D	
	Establish internal agreements with collaborating units/internal partners.	A	D	
	Ensure that monitoring of the trial is conducted and followed up.	A	D	A
	Ensure that written agreements are made with all new collaborating parties/institutions.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Establishing and Maintaining Study Files	Create a Trial Master File (TMF) for the trial and an Investigator's Site File (ISF) at each individual study site.	A	D	
	Keep the TMF updated with relevant information.	A	D	
	Keep the ISF updated with relevant information.			A
	Conclude and archive the clinical trial, EQS IDs 32429 and 32435.	A	D	A
	Ensure that the electronic systems used for archiving	A	D	A

	comply with internal procedures.			
	Maintain an overview of where the trial documentation is stored.	A		A

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Risk Assessment	Conduct a risk assessment.	A	D	
	Ongoing risk assessment of the trial.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Training and Initiation	Ensure necessary training for all investigators and study personnel in accordance with the protocol and guidelines for each trial.	A	D	
	Prepare a written overview of task delegation to study personnel.			A
	Oversee individuals or parties to whom the principal investigator has delegated study-related tasks or functions, and ensure that they are qualified for the tasks and functions they have been delegated.			A
	Provide necessary training for all new investigators and study personnel in the protocol and study-specific guidelines.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator

Data Processing	Develop a data management plan.	A	D	
	Adhere to the data management plan.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Statistics	Develop a Statistical Analysis Plan.	A	D	
	Adhere to the Statistical Analysis Plan.	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Handling of Investigational Product	Ensure supply of medicine when needed.	A	D	
	Ensure that the investigational product, including comparison preparation with any associated equipment, is made available to the subject free of charge	A	D	
	Provide adequate investigational preparation throughout the trial	A	D	

Flowchart	Task	Sponsor (institution)	Coordinating Investigator	Principal investigator
Alerts and reporting	Ensure information to the ethics committee and authorities through CTIS about first patient recruitment, end of study nationally, end of study for entire study, suspension, non-significant changes to protocol, etc. *New legislation*	A	D	

	Report serious non-conformities to the authorities *New legislation*	A	D	
	Assess serious adverse events (SAEs) and report Suspected Unexpected Serious Adverse Reaction (SUSAR) to authorities through EudraVigilance, and an ongoing assessment of the benefits and risks of conducting the trial. Send annual report. Inform all PI of serious and/or unexpected suspected adverse reactions	A	D	
	Update registries and ahus.no/helsenorge.no when the trial has stopped inclusion of study participants, EQS ID 34316	A	D	
	Report nonconformities in accordance with Sponor's guidelines for nonconformity reporting and in accordance with the enterprise/institution's internal routines, EQS ID 34152 and 34153		A	A
	Send final report to REC and report to SLV *Old legislation*	A	D	