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Guidelines for Good Operational Practice

Guidelines for Good Operational Practice for the Swiss CTU Network and SAKK

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In collaboration with



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Abbreviations

AE	Adverse Event
CA	Competent Authority(ies)
CAPA	Corrective And Preventive Actions
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTU	Clinical Trial Unit
EFQM	European Foundation for Quality Management
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HMG	Heilmittelgesetz
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee(s)
I(M)P	Investigational (Medicinal) Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISO	International Organization for Standardization
MedDev	Medical Devices
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
RA	Regulatory Authority(ies)
SA(D)R	Serious Adverse (Drug) Reaction
SAE	Serious Adverse Event
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SCTO	Swiss Clinical Trial Organisation
SLA	Service Level Agreement
SOP(s)	Standard Operating Procedure(s)
SUSA(D)R	Suspected Unexpected Serious Adverse (Drug) Reaction
TMF/SMF	Trial Master File / Study Master File
VKlin/Oclin	Verordnung über klinische Versuche mit Heilmitteln (VKlin) / Ordonnance sur les essais cliniques de produits thérapeutiques

Note: For definitions of terms please refer to the Glossary in the Annex.

Introduction

Clinical Trial Units (CTUs) are organisations established for the conduct of clinical studies with staff specialised in clinical research. In Switzerland, they are public organisations, initiated through a unique partnership between the Swiss National Science Foundation (SNSF), the universities, and the (university) hospitals in order to improve and advance academic clinical research.

They have the common objective to provide services to their customers in academic clinical research while meeting the legal requirements and ethical standards.

Therefore, their missions are diverse, and they have a wide range of tasks including:

- Advising customers on designing and conducting clinical studies, including submission to independent ethics committees and regulatory authorities
- Providing customers with the methodological and logistical support required to perform clinical studies, e.g. the recruitment of study subjects, technical support, access to investigator networks
- Conducting clinical studies in collaboration with and on behalf of customers
- Providing training for clinical research staff

The SNSF also initiated the foundation of the Swiss Clinical Trial Organisation (SCTO) as the umbrella organisation for Swiss clinical research. Currently, within the SCTO, all Swiss SNSF-funded CTUs are associated in a network of academic clinical research centres. The SCTO has the mandate to coordinate and facilitate the cooperation between the CTUs, mainly with respect to (but not limited to):

- Specification of quality standards
- Continuing education
- Intermediation of national and international multi-centre studies

Regarding the harmonisation of quality standards, all CTUs and the associated network Swiss Group for Clinical Cancer Research (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung, SAKK) have jointly developed a Quality Policy under the lead of the SCTO. In this Quality Policy of the CTU Network, the groups mentioned above commit themselves to aligning their own CTU management systems in accordance with applicable national and international regulatory requirements, with the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP), and with internationally acknowledged process-oriented standards for quality management systems (QMS).

Objectives

The Guidelines for Good Operational Practice of the Swiss CTU Network give guidance on the implementation of its Quality Policy with a view to reaching the following aims:

- Harmonisation of professional practices within the CTU Network
- Continuous improvement of quality and performance of CTUs
- Continuous improvement of the quality of clinical investigations
- Common reading base for CTU staff members and customers
- Recognition of the expertise of the CTUs on a national and international level

Regulatory Framework

The Guidelines for Good Operational Practice of the Swiss CTU Network are in accordance with applicable national and international law, regulatory requirements, and ethical guidelines and regulations.

The current regulatory repositories provide a clear and defined regulatory framework for the conduct of clinical studies regarding subjects' safety, ethical principles, and data quality. In addition, the QMS, which is implemented at the individual CTUs, is based on internationally recognised models, such as e.g. ISO 9001:2008¹ or the EFQM Model².

¹ ISO 9001:2008, Quality management systems – Requirements

² Model for Business Excellence of the European Foundation for Quality Management

Scope

The Guidelines for Good Operational Practice represent a framework of common standards for professional and operational practice at Clinical Trial Units. It applies to activities relating to the management of the CTUs as organisations as well as to clinical research project management at the individual CTUs.

As a common standard of the CTU Network, the Guidelines are recommended for implementation at SNSF-funded CTUs and associated networks. It is, however, within the competence of each CTU to adopt these Guidelines depending on the specific needs of the individual organisations. The organisational environment of the superordinate organisations, e.g. (university) hospitals, particular objectives, size and organisational structure of the individual CTU as well as their financial and human resources, respectively, may considerably influence these needs. Besides, implementation may also be influenced by the type of research projects (e.g. HMG versus non-HMG studies) and the type of study related activities offered by the individual CTU or organisation.

In addition, the implementation of the Guidelines needs to consider the general conditions and specificities of investigator initiated studies. With this in mind, the Guidelines should not only serve to guarantee subject safety and excellent data quality, but also to maintain high flexibility to adapt to the needs of individual projects, to challenge unnecessary regulatory hurdles and to ensure the careful use of restricted academic budgets. This can be reached through the application of risk based strategies, which should be carefully adapted to the specific requirements of individual research projects.

Structure

The Guidelines for Good Operational Practice are divided into two parts.

Part I focuses on the management of the organisation. These chapters highlight its structure, its internal functioning, resources, and anything that may have an impact on the activities of the CTUs.

Part II focuses on the main service provided by the CTUs, namely the management of clinical research projects. These chapters highlight the requirements for the design, preparation, implementation, and development of clinical research projects carried out or supported by the CTUs.

Each chapter lists requirements, which are deemed necessary for the good operational functioning of a CTU. The requirements are specified by detailed criteria, responsibilities, processes, objectives etc. (as applicable), listed as bullet points. These specific elements explain how to ensure said requirements are fulfilled.

Definitions for the most important specific terms are included in the Glossary in the Annex. They are highlighted in bold, when used for the first time in the context.

Whenever the masculine gender is used, both men and women are included, unless otherwise stated.

Update

The Guidelines for Good Operational Practice of the Swiss CTU Network will be updated by the SCTO in collaboration with the CTUs and the associated networks if there is any major regulatory change or evidence for improvement, and their relevance and accuracy will be reviewed every second year.

Management of the Organisation

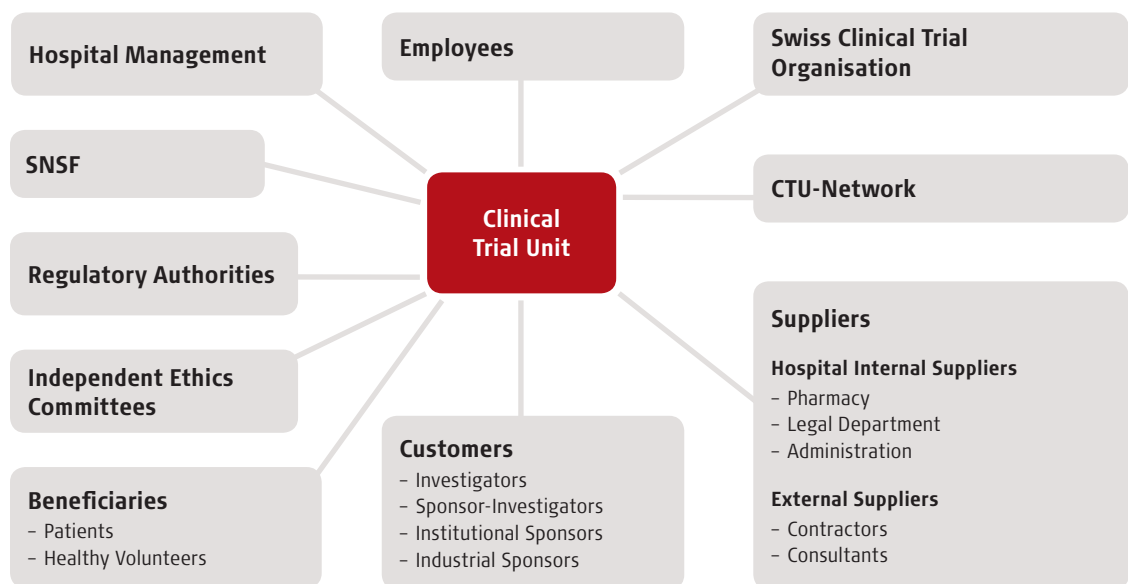


Figure 1: Typical Stakeholders of a CTU

As stated in the Introduction, a **Clinical Trial Unit (CTU)** is a Swiss centre for academic clinical research fostered by the **Swiss National Science Foundation (SNSF)**. It is an **organisation**, which is publicly funded to provide high quality services to its **customers** in the field of clinical research. As a service provider, the CTU has the expertise and the **processes** in place to support its customers in any aspect of the conduct of a **clinical study**, from study design to publication of study results.

Depending on its legal entity, size and structure, each CTU defines its own scope, its limitations, its stakeholders (see Figure 1) as well as its activities and responsibilities.

However, in order to successfully lead and run any organisation, it is necessary to direct and control it in a systematic and transparent way. Success can result from implementing and maintaining a **management system** that is designed to continually improve performance, while addressing the needs of all interested parties. Managing an organisation encompasses **quality management (QM)** amongst other management disciplines.

The various parts of an organisation's management system might be integrated together with the quality management system (QMS) into a single management system using common elements. This can facilitate the planning, the allocation of resources, the definition of complementary objectives, and the evaluation of the overall effectiveness of the organisation.

The QMS is the part of an organisation's management system that focuses on the achievement of results in relation to the quality objectives, to the satisfaction of the needs, and to the expectations and requirements of interested parties, as appropriate. The quality objectives generally complement other objectives of the organisation, such as those related to growth, funding, profitability, the environment, and occupational health and safety.

Relationship between Quality Management Systems and Excellence Models

It is desirable that the implemented QMS should follow a process approach. The approaches of quality management systems given by the **International Organization for Standardization (ISO)** in the ISO 9000 family of standards and in other organisational excellence models (e.g. the model given by the **European Foundation for Quality Management, EFQM**) are based on common principles, which are:

- a) To enable an organisation to identify its strengths and weaknesses
- b) To contain provision for evaluation against generic models
- c) To provide a basis for continual improvement
- d) To contain provision for external recognition

The difference between the approaches of the quality management systems in the ISO 9000 family and the excellence models lies in their scope of application. The ISO 9000 family of standards provides requirements for quality management systems and guidance for performance improvement; evaluation of quality management systems determines fulfilment of those requirements. The excellence models contain criteria that enable comparative evaluation of organisational performance and this is applicable to all activities and all interested parties of an organisation. Assessment criteria in excellence models provide a basis for an organisation to compare its performance with the performance of other organisations.

It lies within the responsibility of each organisation to define which model shall be used as a basis for their QMS.

1 Strategy and Management Responsibilities

The management strategy shall provide the focus of an organisation. It shall ensure the durability and development of the activities. It anticipates the scientific and political developments while meeting the requirements of its **regulatory authorities (RA)**, customers and **suppliers**.

1.1 Strategy

The top management shall establish and maintain a management strategy to fulfil the mission and objectives of the organisation.

- The top management/steering body defines the strategic directions
- It holds meetings at fixed intervals to discuss strategic decisions
- It validates the strategy at fixed intervals
- The activities of the top management/steering body are documented
- Reports are distributed to all the personnel involved

1.2 Management Responsibilities

Through leadership and actions, the top management shall create an environment where people are fully involved and in which a QMS can operate effectively. The responsibilities of the top management include the following, but are not limited to:

- Ensuring availability of resources (facilities, infrastructure, financial and human resources) in order to meet the legal, ethical and customer requirements
- Implementing a QMS that guarantees:
 - A clear definition of the structure, the processes and **procedures** within the CTU
 - A good internal and external communication
 - The identification and elimination of non-conformities
 - A suitable documentation and records to ensure traceability
 - The competence of the personnel
 - A good business relationship with suppliers and partners
- Ensuring the focus on legal, ethical and customer requirements throughout the organisation
- Establishing and maintaining the Quality Policy and Quality Objectives of the organisation in accordance with the strategy and in consultation with the steering body
- Promoting the Quality Policy and Quality Objectives throughout the organisation to increase awareness, motivation and involvement
- Ensuring that appropriate processes are planned, implemented and monitored which enable the organisation to fulfil the specifications of the services and/or the requirements of the customers and other interested parties and to recognise and eliminate non-conformities, respectively
- Performing periodical review and assessment of the effectiveness and of the suitability of the Quality Policy and Quality Objectives, of the resources, of the processes, of the specifications of the services and of the implemented QMS
- Ensuring that corrective and preventive actions are taken and reviewing their effectiveness

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- 1.3 Communication** The top management shall ensure that the information needed for the organisation to operate and to achieve its objectives is well understood and received on time, both on internal and external levels.
- 1.3.1 Internal Communication** The top management shall define and implement efficient processes for the communication with its staff regarding the effectiveness of the QMS (policy, requirements, objectives and results related to quality and the organisation).
- Tools should be identified and made available to the staff to facilitate the flow of information within the organisation: e.g. team meetings, individual interviews, bulletin boards, internal newsletters, audiovisual/electronic devices, etc.
 - The language of communication and documentation should be selected according to their purpose and their target audience.
 - The frequency of communication and the type of communication tools should be defined.
 - The transmission of information should be recorded.
 - The communication channels between entities (units, departments) should be established.
- 1.3.2 External Communication** The top management shall define a communication policy, which ensures that effective means of communication with partners as well as the public are established and implemented.
- The communication target groups should be identified: e.g. customers, suppliers, CTU Network, scientific community including academic researchers, clinicians, supervisory authorities, etc.
 - The suitable information channels for the respective target groups should be established.
 - Strict **confidentiality** regarding customer **projects** (e.g. scientific data, **subject** data) should be respected.
 - Processes for communication modalities with the public should be established (e.g. publications, advertisements, newsletters, etc.).
 - A special communication plan should be established for emergency situations (e.g. communication with the media in case of subject safety issues).
 - Implemented or released communications should be tracked.

2 Quality Management System

The CTU shall establish, document, implement, and maintain a quality management system (QMS) and continually improve its effectiveness. To this end, the QMS shall be based on the current process-oriented international standards.

2.1 Quality Policy and Quality Objectives

Based on the strategy of the organisation, the top management shall establish and document a Quality Policy and Quality Objectives in order to provide a focus to the organisation. The policy and the objectives shall determine the desired results and assist the organisation in efficiently applying its resources to achieve these results. The legal, ethical and customer/service requirements should be taken into consideration.

- The Quality Policy should outline the general quality criteria and objectives appropriate to the purpose of the organisation and should be in compliance with the Quality Policy of the CTU Network.
- It should provide a framework for establishing and reviewing detailed Quality Objectives.
- It should entail a commitment to comply with requirements and continually improve the effectiveness of the QMS.
- The Quality Policy should be distributed among the staff members of the organisation.
- It should be reviewed for continuing suitability.
- Detailed Quality Objectives should be established for relevant functions and at relevant levels. They should be directly or indirectly measurable and consistent with the Quality Policy.
- The Quality Policy should take into account the results of the different process assessments and measurements.

2.2 Quality Manager

The top management shall delegate the responsibility for and authority over the QMS to a qualified person (Quality Manager, Quality Assurance Manager, Q-Manager).

- The Quality Manager should possibly be independent from operational workflows and reports directly to the CTU Head.
- The Quality Manager is responsible for planning and supervising the QMS.
- The delegation of these responsibilities should be described in a document, e.g. job description, engagement letter.
- The Quality Manager should have documented knowledge and skills to perform his tasks.
- The Quality Manager should be allowed to access training that enables him to expand his knowledge and to improve his skills.

2.3 Identification of Processes

The processes and their application throughout the organisation shall be determined and documented. They generally include management responsibilities/activities, **product** or service realisation, measurement, analysis and improvement.

- The processes identified should be integrated into or linked to the QMS of the superordinate organisation, e.g. the (university) hospital, if applicable.
- The internal and external customers for each of these different processes should be identified.
- The sequence and interactions of these processes should be defined and documented.
- Criteria and methods should be determined which ensure that both the operation and control of these processes are effective.
- The availability of the resources and information necessary to support the operation and monitoring of these processes should be ensured.

2 Quality Management System

- The processes should be monitored, measured and analysed, where applicable. If corrective or preventive actions are necessary to achieve the planned results and to continually improve the processes, these measures should be reviewed for effectiveness after implementation.
- If any process is outsourced that could affect the conformity to requirements of any service, the control over such processes should be ensured and defined in the QMS.

2.4 Quality Management Documentation

The Quality Manual shall describe the purpose, the legal basis, the leadership and management processes, as well as the allocation of resources and responsibilities for the quality-relevant processes. This document should be in line with the Quality Policy of the CTU Network.

- The Quality Manual describes the scope of the QMS.
- It includes the **documented procedures** established for the QMS, or references where they can be found.
- It includes a description of the interaction between the processes of the QMS as well as the attribution of resources and responsibilities for quality relevant processes.
- The Quality Manual is a controlled document as defined in Chapter 2.5, Control of Documents and Records.
- The CTU Head approves the Quality Manual.
- The frequency of review of the Quality Manual should be defined in the QMS.

Appropriate quality management documentation should be in place, as it is necessary for the effective planning, operation and control of processes and activities.

Note: The size and extent of the quality management documentation varies from organisation to organisation, depending on its size, the complexity of its activities, and the competence of its personnel. The documentation can have any form and be of any type of medium. Generally, the quality management documentation includes:

- Documents describing the Quality Policy and Quality Objectives
- A Quality Manual
- Documented procedures and records of all processes required by international quality management standards
- Other quality-relevant documented procedures and records of the processes (forms, worksheets, etc.) as determined by the CTU (e.g. customer related processes)

2.5 Control of Documents and Records

Documents and records required by the QMS shall be controlled.

- Documented procedures for the overall life cycle of key documents should be in place. They should define the controls needed for:
 - Approval prior to issue
 - Regular review and update, and re approval
 - Identification of changes and current revision status (version control, archived versions)
 - Availability of relevant versions of documents at points of use
 - Guarantee of legibility and easy identification
 - Guarantee of identification of internal and external documents
 - Prevention of unintended use of obsolete documents (password protected access only by Quality Manager or designated personnel)
- Documented procedures for the identification, storage, protection, retrieval, retention and disposition of records should be established.
- Records should remain legible, identifiable and retrievable for defined time periods.

- If the procedures are based on processes of other, superordinate organisations, e.g. the (university) hospitals, they may be referenced as such in the documentation system.
- If procedures other than those of the CTU are applied, this should be documented.
- Competent persons should review the quality documents to ensure their compliance with applicable rules and regulations.

2.6 Management Review

The top management shall review the entire QMS at planned intervals in order to measure the organisation's present efficiency, its effectiveness and level of performance. Moreover, this review shall enable the top management to assess opportunities for improvements and the need for changes in the QMS. The following parameters should be taken into consideration:

- Changes within the structure of the organisation
- Results of internal audits/self assessments and external audits
- Customer evaluations, positive feedback, and complaints
- Key indicators of the process performances
- Results from service conformity assessments
- The status of the corrective actions plan and of the follow-up actions from previous management reviews and/or assessments
- Internal suggestions for improvement

2.7 Risk Management

The CTU shall have a policy and a plan for the assessment and management of risks by the organisation. International standards like ISO 31000¹ may be used as a basis for the implementation of an adequate risk management.

- The risk management policy should be defined by the CTU Head and/or the Quality Manager and distributed among the staff.
- This policy should outline general objectives as well as the resources made available to achieve them.
- The responsibilities in terms of risk management should be identified at appropriate levels.
- A risk management plan should be developed and implemented.
- Measures should be taken to ensure the monitoring and evaluation of the effectiveness of the risk management plan.

¹ ISO 31000:2009: Risk Management – Principles and guidelines

3 Management of Resources: Infrastructure and Working Environment

The top management shall ensure the suitability and security of the infrastructure and the working environment, including technical equipment and computerised systems.

3.1 Infrastructure

The CTU shall ensure the maintenance of its entire infrastructure in accordance and in collaboration with the superordinate organisation, e.g. the (university) hospital, if applicable.

- A responsible person for managing the CTU relevant infrastructure should be identified. He is the contact person for the technical department of the hospital, if applicable.
- Periodically, a risk analysis should be performed, based on the results of which the following points should be checked/established:
 - A list of the study relevant infrastructure and equipment should be drawn up and updated on a regular basis.
 - Critical facilities should be identified and a proper security system put in place.
 - Critical equipment should be stored in facilities with restricted access.
 - Preventive maintenance of equipment should be planned and carried out as appropriate.
 - An annual maintenance table for all equipment should be established and kept up to date.
 - Maintenance **contracts** should be concluded with the service departments of the supplier.
 - Periodic equipment checks should be conducted as recommended by the supplier.
 - Records of the interventions made on equipment, premises, and materials should be kept throughout their lifetime.

3.2 Working Environment and Safety

The hygiene standards and safety requirements for the working environment (facilities, equipment) should be defined, if applicable, in accordance with the respective department of the superordinate organisation, e.g. (university) hospital.

- Maintenance of the CTU premises and equipment should be ensured, and checks thereof conducted.
- The guidelines on hygiene and safety should be available to all staff members.
- The staff should be familiar with the existing hygiene and safety rules and regulations.
- Documented procedures describing how to proceed in the case of fire or accidents should be in place.
- Periodic evaluations of the understanding and implementation of these rules and regulations should be conducted.

3.3 Security of Computerised Systems

The security of computerised systems should be ensured, if applicable, in collaboration with the respective department of the superordinate organisation, e.g. (university) hospital. For details refer to the SCTO Data Management Guidelines.

4 Management of Resources: Human Resources

The top management shall ensure the availability of the human resources needed for the efficient and correct performance of all service-related activities, the implementation, maintenance and continual improvement of a QMS, as well as for enhancing customer satisfaction. Responsibilities and authorities shall be defined and transparently communicated within the organisation.

4.1 Management of Human Resources

Personnel shall be competent on the basis of appropriate education, training, skills, and experience. A recruitment policy defines how to refine, polish, and develop the staff skills.

- The necessary competence of the personnel to perform any tasks related to the services provided should be determined.
- If applicable, training should be provided in order to achieve the necessary competence.
- Personnel should be aware of the relevance and importance of their activities.
- They should know how to contribute to the Quality Objectives.
- All personnel should be trained in the internal procedures.
- Documentation of internal and external training courses should be filed.
- The infrastructure and work environment should be conducive to achieving conformity to the service requirements (see Chapter 3.2, Working Environment and Safety).

4.2 Employment

- Each staff member should have an employment contract in accordance with regulatory requirements.
- Each staff member should have a job description documenting the duties and responsibilities of his position. The document is updated at any major change of mission, position or function.
- A personal record file for each staff member should be kept updated by the CTU management or the respective Human Resources department at the superordinate organisation, e.g. (university) hospital.
- The line manager should conduct an annual assessment interview with each staff member. The modalities for conducting such an interview should be specified in writing.

4.3 Organisational Chart

An organisational chart shall reflect the organisational structure including functions.

- The organisational chart should be updated with any relevant change in the organisation, normally at least once a year.

4.4 Staff Training and Integration

Professional training and continuing education shall be promoted and supported.

- A documented procedure should describe the integration of new staff.
- A training plan for the first period should be established in order to ensure the new staff is trained on his duties.
- For all employees, annual training goals should be defined.
- The training courses attended by the staff should be recorded.

4.5 Interns / Volunteers

The recruitment and training of interns/volunteers shall be supported.

- Partnerships may be established with training organisations providing training in clinical research activities.
- An intern admission policy should be defined. The internship objectives should be defined.

5 Management of Resources: Financial Management

A financial management system shall allow the assessment and planning of the resources needed for the smooth running of an organisation and for the sustainability of its activities.

- The CTU should be considered a full management unit, so that the expenses generated by the CTU and covered by the superordinate organisation, e.g. (university) hospital and the SNSF can be clearly identified.
- The frequency of exchange of information between the financial services of the CTU, the superordinate organisation and the SNSF should be defined.

6 Management of Resources: Purchasing and Suppliers

At any time, the CTU shall have the resources needed for the proper implementation of research projects, in compliance with the purchasing rules and regulations. If the purchasing procedures are based on processes of superordinate organisations, e.g. (university) hospitals, they may be referenced as such in the documentation system.

6.1 Order Process

- Basic equipment and material (e.g. office material, etc.) should be ordered in accordance with the guidelines of the organisation.
- Project specific purchases should be allocated to the relevant project through the specifications and/or purchase orders.
- The order process should be formalised in a documented procedure.

6.2 Suppliers

- The suppliers should be selected and assessed for their impact on the services (e.g. research projects), and their ability to meet the specified needs.
- A documented procedure for the evaluation of suppliers should be in place.
- Contracts with suppliers and audits to verify the quality of the suppliers may be applicable for specific research project related equipments/services (e.g. electronic data capturing software).

7 Change Management

The CTU shall ensure that processes are defined for the communication and the assessment of any changes (and the implementation thereof, if applicable), which have a potential impact on the services provided by the organisation.

- A documented procedure should be in place for the change management, including changes in CTU internal processes and/or the QMS, as well as changes in the legal, ethical, and regulatory framework.
- A responsible person (usually the Quality Manager) should be appointed to ensure that any changes are monitored.
- The regulatory monitoring should be conducted through identified information sources allowing the screening of national and international laws and regulations applicable to the CTUs.
- For any change, the responsible person has to carry out an impact assessment. He has to determine if the QMS, the documentation or the working methods need to be adapted.
- According to the relevant process and assessed impact of the change, the Quality Manager may set up a task force to update the appropriate documents.
- It should be ensured that everybody concerned is informed about any implemented changes.

8 Measurement, Analysis and Improvement

The top management shall plan and implement the monitoring, measurement, analysis and improvement procedures needed to demonstrate the conformity of the service realisation processes, the conformity of the QMS and the continual improvement of the effectiveness of the QMS.

8.1

Customer Satisfaction

The determination of customer requirements and the evaluation of the customer satisfaction are considered good tools to improve the customer-related processes.

- Information from customers may be collected and analysed (e.g. satisfaction surveys, complaints and claims made during projects).
- The analysis of the positive points of a survey (criteria for satisfaction) allows the capitalisation of the know how.
- The analysis of average or negative points (criteria for dissatisfaction) enables establishing corrective actions for future projects.
- The needs of the customers should be anticipated and included in the design of future projects or other services.

8.2

Audits

Self Assessments

Audits shall be used to determine the extent to which the QMS requirements are fulfilled.

- Internal audits/self assessments should be planned and performed to check and improve the efficiency of the QMS.
- The management of internal audits and/or self assessments should be described in a documented procedure.
- A schedule defining the frequency, scope, methodology and responsibilities for internal audits and/or self assessments should be established, and the Quality Manager should track its implementation.
- External audits may be integrated into the schedule.
- Auditors should be independent of the audit process and shall not audit their own work.
- For any audit findings, Corrective And Preventive Actions (CAPAs) should be planned and implemented by the responsible line manager.
- All audit findings and CAPAs should be analysed and used to assess the effectiveness of the QMS and to identify opportunities for improvement.
- Records of audits and CAPAs should be maintained.

8.3

Measurement and Analysis of Processes and Services

A periodical analysis of the effectiveness of the QMS shall ensure that the processes and the services are adequate. It is important to determine, collect and analyse relevant data to demonstrate the suitability of management and service processes.

- The key indicators related to the process performance should be defined, systematically documented and evaluated.
- Analysis of data should include data from monitoring and measurement as well as other relevant sources and provide information pertaining to:
 - Customer satisfaction
 - Conformity of services and products
 - Characteristics and trends of services and products, including opportunities for preventive actions
 - Suppliers
- If applicable, improvement measures should be determined and implemented by the management.

8.4**Control of
Non-conformities**

Services and/or processes, which do not conform to the requirements should be identified and controlled to prevent unintended use or delivery.

- A documented procedure for dealing with non-conformities should be in place, including the respective responsibilities.
- This procedure describes the actions to be taken to eliminate and prevent the detected non-conformities.
- It describes actions to be taken if the customer detects non-conformities of services after delivery (complaints).
- When non-conforming services are corrected, a re-evaluation to prove conformity is necessary.

8.5**Continual Improvement
Corrective Actions
Preventive Actions**

Corrective actions should be taken to eliminate the causes of non-conformities in order to prevent recurrence. Correspondingly, preventive actions should be defined to prevent the occurrence of potential non-conformities.

- The processes should be formalised in documented procedures for:
 - Managing non-conformities (including customer complaints) and potential non-conformities
 - Determining the causes for (potential) non-conformities
 - Evaluating the need for corrective and preventive actions
 - Determining and implementing actions needed
 - Recording the results of the actions taken
 - Reviewing the effectiveness of the actions taken

Management of Clinical Research Projects

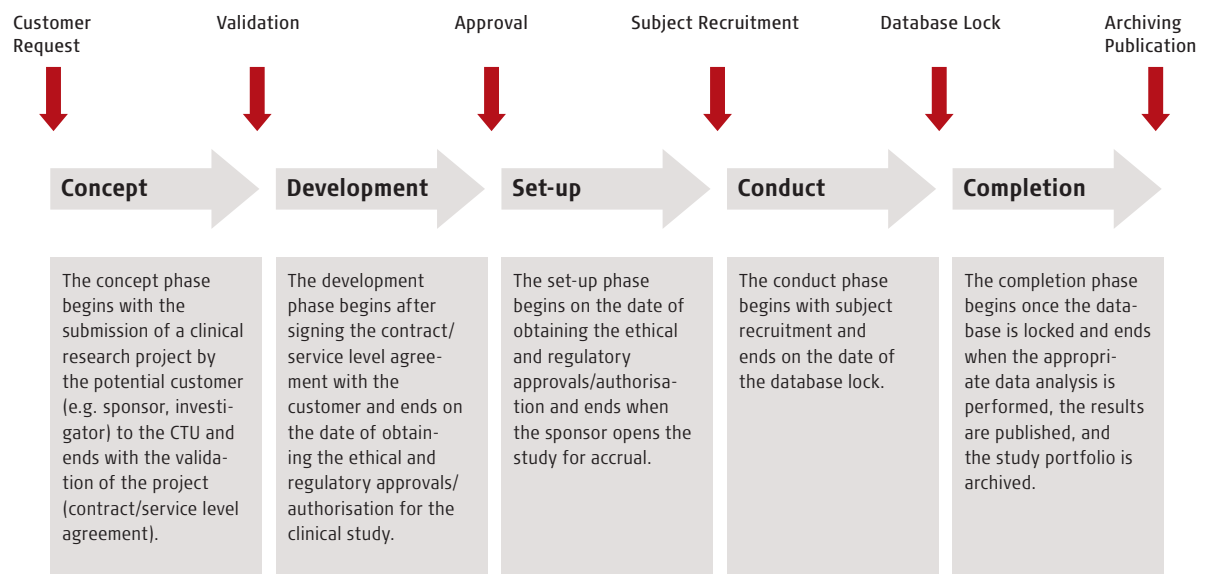


Figure 2: Phases of Clinical Study Projects

Each CTU offers diverse services and performs diverse activities. However, the main service process of all Swiss CTUs is providing support for the planning and conduct of clinical studies.

In general, the CTU assumes the role of an academic **contract research organisation (CRO)**, but it can also assume the **sponsor's** responsibilities or provide services related to the **investigators'** or **sponsor investigator's** activities and responsibilities¹.

Depending on its role in each project, the CTU performs the described activities or provides support and advice to carry out the activities in accordance with the applicable legal and regulatory requirements.

The CTU can provide services for the overall management of clinical studies or only provide specific support for partial sub processes. According to **Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP)**, all tasks delegated by the sponsor should be specified in writing. Thus, the CTU and the customer should define the scope of each individual research project in a contract and/or **service level agreement (SLA)**. However, the ultimate responsibility for the quality of the study and the integrity of the data remains with the sponsor.

In the following part of this document, the main requirements for the activities in the conduct and management of clinical studies are detailed following the course of a clinical study project. Said requirements are listed according to the phases of a study project, as defined in Figure 2. Depending on the study project, activities may be performed in another sequence and therefore be attributed to different phases.

1 Often, a clinical research project is initiated and managed by an academic investigator in a university hospital, but financed by another institution, such as a research foundation, or a pharmaceutical company. In that case, the "sponsor" is the investigator (called an sponsor-investigator). Note, that this differs from common parlance, where the "sponsor" is the person or organisation, who pays. For ICH GCP definitions of "sponsor" and "sponsor-investigator" refer to the Glossary in the Annex.

9 Concept Phase

The concept phase begins with the submission of a clinical research project by the potential customer (e.g. sponsor, investigator) to the CTU and ends with the validation of the project (e.g. contract, service level agreement).

The objective of this phase of a project is the evaluation of the feasibility and the capacity of the CTU to perform and/or to co ordinate the proposed study project, or to carry out the specified tasks within the project. The CTU should designate a responsible person/contact person for the evaluation phase of the project.

9.1 Project Evaluation

To evaluate the feasibility of a study project, the potential customer should provide as much information as possible and available:

- Project description or briefing (e.g. study outline, including timeframe, task list, etc.)
- **Protocol** or synopsis, if already existing
- **Investigator's brochure (IB)** and **investigational medicinal product dossier (IMPD)**, if available and applicable
- Confidentiality agreement between customer and CTU, if applicable

9.1.1 Scientific Aspects

Based on predefined criteria, the CTU should evaluate the submitted clinical research project regarding the scientific aspects, as for example:

- Relevance, originality, and scientific quality of the project
- Expected impact in terms of public health
- Potential valorisation of results (e.g. publications, patents)
- Methodological quality and innovation
- Academic research projects should be prioritised

9.1.2 Project Assessment

If the scientific evaluation results in a positive preliminary decision of potential interest, a more detailed assessment of feasibility should be performed.

Based on the task list agreed on with the customer and on the provided information, the CTU should evaluate the following aspects regarding the study management and clarifies open issues with the potential customer, if required:

- The project feasibility within the CTU regarding e.g. the size of the project, the budget, available human resources, equipment
- Timelines (customer expectations)
- Project-specific risk analysis regarding subject safety and data quality, e.g. HIV, radio-actives, biological contamination, etc.
- Budget (expected costs for the CTU/site), financing (e.g. funding, grants)
- Availability of the investigational product
- Availability of potential subject pool at the site(s)
- Availability of study team (e.g. potential GCP trained investigators, study nurses, etc.)
- Safety management, pharmacovigilance
- Data management and statistics
- Appropriateness of facilities at study site(s)
- Feasibility of contracts and authorisations, including intellectual property (in collaboration with the legal department of the hospital or with any third parties)
- Subject insurance, investigator indemnification
- Legal permissions, e.g. for radio-actives, etc.
- Publication policy
- Conflict of interest policy
- Registration of the study in a publicly accessible database

9.1.3 Conclusion	<p>If the CTU is not willing or able to get involved in the project, the customer should be informed about this decision as soon as possible.</p> <p>If the CTU is willing and able to accept the project, a quote should be submitted. After reaching a mutual agreement, the contract and/or the service level agreement is prepared.</p>
9.2 Contracts and Authorisations	<p>A quote and – after acceptance by the customer – a corresponding contract should be established to define the responsibilities and authorisations. The CTU should decide if the contract can be drawn up and signed directly with the customer, or if suppliers and other hospital internal departments should be involved as partners.</p>
9.2.1 Overall Budget	<p>An estimated overall budget for the research project should be established. Collaboration with potential external partners should be taken into consideration.</p>
9.2.2 Contracts and Service Level Agreements	<p>The necessary legal framework for the research project should be established in collaboration with the legal department of the hospital or any third party, as applicable.</p> <p>Note: All responsibilities a sponsor delegates to e.g. a CRO, pharmaceutical company for study drug supply, etc. should be specified in writing, i.e. covered in a contract and/or a SLA [ICH GCP Art. 5.2.2].</p> <ul style="list-style-type: none"> • All tasks delegated to the CTU and all planned timelines should be covered by a contract/service level agreement (SLA). • A process for handling agreements and contracts, from their development to their approval, should be defined. • Liability and other insurance issues should be clarified, including the nomination of a Swiss legal representative of the sponsor [VKlin Art. 7,3], if applicable. • Specimens/drafts of contracts with investigators, centres, CROs, pharmacies, suppliers, etc. should be prepared. • Confidentiality agreements should be drafted for investigators/suppliers. • All agreements and contracts, as required depending on the study type, should be tracked. • All these procedures should be tracked and recorded.
9.2.3 Intellectual Property	<ul style="list-style-type: none"> • Ownership of intellectual property should be defined, including publication rights and patenting.
9.2.4 Conflict of Interest Policy	<ul style="list-style-type: none"> • The conflict of interest policy for the investigators should be discussed with the customer. • Potential conflicts of interests of the CTUs should be assessed and made transparent. • Draft documents for financial disclosure and/or disclosure of interests of investigators should be prepared according to national laws.

10 Development Phase

The development phase begins after signing the contract / service level agreement with the customer and ends on the date of obtaining the ethical and regulatory approvals/authorisation for the clinical study.

The objective of this phase is to plan the necessary resources for the project and to prepare the required processes and the documents for submission to the **independent ethics committees (IEC)** and regulatory authorities, if applicable.

10.1

Project Management

10.1.1 Project Team

The optimal management of the research project should be ensured. For large projects, a multi-professional project team may be composed and a project manager be nominated.

The following points should be taken into consideration:

- The project team should have all the skills needed to manage the research project.
- Tasks and responsibilities within the project team should be clearly defined and recorded in a document (task allocation list).
- The communication and reporting processes should be defined and documented.
- Delegation of responsibilities within the project group and with respect to the customer should be documented and communicated to the project team members.
- A project kick-off meeting may be held with all project team members and representatives of all involved departments.
- The cornerstones of the project should be summarized in writing (e.g. in a project initiation document) and distributed to all involved parties.

10.1.2

Timelines

In collaboration with the customer, specifications and milestones should be defined and realistic project timelines should be set.

- The project timelines should be defined and captured in an overview.
- Timelines for all involved parties should be specified.

10.1.3

Human Resources

- Appropriate personnel should be identified and the availability of the appropriate skilled staff ensured.
- Availability of potential GCP-trained investigators should be identified.
- Training should be planned, if necessary.

10.1.4

Budget

In collaboration with the customer, the detailed financial plan for the project should be established, based on the estimated overall budget.

- The budget for all costs of involved parties in relation to the study project should be drawn up.
- The cost estimates should be captured, including investigators' fees, database costs, CROs (e.g. for monitoring), laboratories, couriers, pharmacy as well as for apparatus to be purchased, etc.
- The call for bids should be distributed to relevant potential service providers and should be tracked.
- Based on the quotes, the costs for potential service providers (e.g. monitoring) should be estimated.
- The terms for payment of allowances and reimbursements for **study subjects** should be determined in relation to the invested time and the experienced constraints. Resulting costs should be estimated.

- Costs for insurance, import fees, etc. have to be clarified.
- Submission fees should be clarified with IEC and RA, if applicable.
- The financial plan should be an integral part of the final contract with the customer.

10.2 Investigator's Brochure

Support for either the overall compilation or the improvement of the investigator's brochure (IB) and investigational medicinal product dossier (IMPD) may be provided. The IB and/or the IMPD shall be assessed regarding their adherence to ethical, regulatory and ICH GCP requirements. In particular, the following points should be checked:

- The IB (and in addition the IMPD, if applicable) should comply with the requirements of ICH GCP Chapter 7.
- Structure and content should comply with the requirements specified in ICH GCP [Art. 7.5].
- If an IB (and, if applicable, an IMPD) already exists, a current version (not more than 12 months old) should be available.
- For marketed products the IB/IMPD is not necessarily needed for submission to IEC and RA, if applicable. It may be substituted by the summary of product characteristics or the product information. However, if a new indication or a new galenic form of marketed products is tested, the IB should be submitted. However, for clinical studies without a commercial sponsor, other **documentation** may in certain cases be accepted, e.g. an expanded section in the background information of the protocol for investigator initiated studies (IIS), or basic product information for marketed products (to be clarified with RA).

10.3 Protocol

Support for either the overall development or for the improvement of the protocol may be provided by the CTUs. Template documents for protocols and/or checklists, e.g. as provided on the websites of Swissethics and/or Swissmedic, should be used.

The protocol shall be assessed regarding its adherence to ethical, regulatory and ICH GCP requirements [Chapter 6], and its feasibility shall be evaluated.

In particular, the project team should check the following points and clarify them in collaboration with the customer, if necessary:

- A clear hypothesis with primary and secondary endpoints should be formulated.
- Methodological choices should be in accordance with the scientific requirements.
- The population to be studied, inclusion/exclusion criteria, subject withdrawal criteria, the method of randomisation (e.g. web-based or using randomisation envelopes) and blinding/unblinding processes should be defined.
- Assessment/evaluation criteria, examinations, and measuring methods should be determined.
- Administration and accountability of investigational products, treatment periods including follow up treatment, and treatment compliance should be described.
- Allowed/prohibited concomitant medication, rescue medication, and procedures for **adverse event (AE)** and **serious adverse event (SAE)** reporting, including follow up of AEs/SAEs should be clearly defined.
- Study-relevant literature and data should be provided.
- Data management and statistics (including sample size calculation) should be well documented, including the timing of planned interim analyses, if any.
- Consistency of protocol, **case report forms (CRFs)** and study subject information should be checked.

10.4 Data Management

If per contract/SLA, data management will be performed by the CTU, the data manager(s) have to be informed about the study details. They should set up a database according to the documented procedures and **standard operating procedures (SOPs)**.

The data manager(s) are responsible for database set-up and validation, data entry, data correction processes, etc.

If requested by the customer, a statistical analysis plan (SAP) should be established, taking into account the overall principles of the data management plan.

For details refer to the SCTO Data Management Guidelines.

10.5 Case Report Forms

Data collection specimens, e.g. case records/case report forms (CRFs), shall be designed in compliance with the protocol, if they are not already provided by the customer. The CRFs may be paper-based or in an electronic form (eCRFs).

- If applicable, the CRF should be developed and validated by a team of qualified persons (e.g. biostatistician, data manager, etc.) in collaboration with the investigator and customer [ICH GCP Art. 5.4.1].
- CRF training for **monitors**, investigators and other study personnel should be planned.
- Good clinical data management principles should be used to translate the objectives of the protocol into the CRFs.

For details refer to Good Data Management Practice Principles as well as to the SCTO Data Management Guidelines.

10.6 Informed Consent Process

Support shall be provided to ensure that the **informed consent** process is in compliance with ICH GCP [Art. 4.8], and ethical and regulatory requirements.

- A documented procedure for the information of study subjects and obtaining informed consent should be developed.
- Template documents and/or checklists should be used to draft subject information sheets and informed consent forms, e.g. as recommended on the websites of Swissethics and/or Swissmedic.
- Special requirements should be fulfilled for studies in emergency situations and studies with minors and legally incapable adults [HMG Art. 55, 56].

10.7 Selection of Study Sites

If not already defined by the customer, study sites should be selected, ideally by feasibility checks performed in an on site pre study visit (selection visit) at each site. Alternatively, a standardised requirement list of criteria can be completed by telephone conference or mail correspondence. The following aspects should be checked:

- The expertise in the respective study field and motivation of the investigators should be evaluated, including qualification, education and experience in study conduct and GCP training (CVs).
- The availability of skilled staff, including back up personnel, should be ascertained (CVs).
- The recruitment potential should be estimated, e.g. based on the data of the last month. Assistance in accelerating/improving recruitment can be offered to the sites by preparing documents, website advertisements, etc.
- The availability of storage facilities for **investigational medicinal products (IMPs)/medical devices (MedDev)** and biological samples should be checked. Access to these facilities should be restricted.
- The availability of study relevant special technical equipment/instruments should be ensured, and a plan for regular checks should be prepared.

- It should be verified that the planned timelines are feasible for all involved parties.
- The selection visits should be documented in writing (selection visit report).

According to the results of the evaluation, the next steps for provision of the necessary items (equipment etc.) should be undertaken. If applicable, the overall budget should be adapted accordingly.

10.8 Logistic Processes

Logistic processes needed for the conduct of the study project shall be identified in accordance with the study protocol. Customer requirements should be defined, described and taken into account, including timelines. The logistic processes encompass:

- Preparation (e.g. packaging, blinding, blistering etc.), supply, distribution, storage and accountability of IMP/MedDev, i.e. from their production release for use in a clinical study to their final destruction, including labelling and temperature control, if applicable
- Handling, storage and shipping of biological samples, including time schedules and shipping instructions, temperature control, availability of containers, equipment, etc.
- Supplying additional study material in collaboration with other departments, if applicable
- Planning of external support for special measurements, such as electrocardiography or other special technical equipment/instruments
- Clarification of the need for and availability of storage facilities
- Preparation of necessary documents

10.9 Evaluation of the Recruitment of Study Subjects

If agreed with the customer, the recruitment of study subjects in accordance with the eligibility criteria described in the protocol shall be planned.

- The process of study subject screening should be clearly defined and working sheets should be developed for documentation.
- The process of study subject selection, as well as collaboration with medical networks, should be described.
- The overall recruitment potential should be actively and formally assessed according to the eligibility criteria and based on the on-site feasibility checks.
- Communication media (e.g. newspaper advertisements, leaflets, posters, internet sites, etc.) adapted to the type of study subjects should be prepared for submission to IEC.
- Quantitative and qualitative indicators for the monitoring of the recruitment process should be identified (by centre and for the overall recruitment across centres).

10.10 Safety Reporting

If it is agreed with the customer, part(s) of safety reporting for IMPs or MedDev, respectively, can be taken over by the CTU. According to this mutual agreement, the following processes shall be planned and formalised in a documented procedure, including details on tasks and responsibilities, preferably by using standard forms:

- Processes for reporting serious adverse events (SAEs) and **suspected unexpected serious adverse reactions (SUSARs)** to the IEC and RA, to the sponsor and to other sites, including timelines for initial information and follow-up as per requirements of the IEC and the RA.
- The process for collection of non-serious AEs.
- The process for the annual safety reporting to IEC and RA.

For details on reporting procedures and timelines refer to the websites of Swissmedic and Swissethics.

10.11 Definition of Randomisation Process	<p>If randomisation has to be performed by the CTU, the randomisation process shall be set up as defined in the protocol. The following points have to be checked:</p> <ul style="list-style-type: none">• The randomisation process should be described in a documented procedure.• The randomisation should be captured on a randomisation list that clearly identifies the subjects by using study specific identification codes. Subject data should be anonymised on the CRF as per regulatory and legal requirements.• A person, preferably a statistician, who is otherwise independent of the study, should produce the randomisation algorithm or list.• The algorithm or list should be stored in a secure and confidential manner.• Procedures for unblinding should be described, if they are not already defined in the protocol.• Randomisation envelopes per site should be prepared, if applicable.• An interactive voice response system or online randomisation functionality may be established, if applicable.
10.12 Quality Assurance	<p>To ensure that the studies are conducted and the data generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements, a quality assurance (QA) and a quality control (QC) system with written SOPs should be implemented and maintained [ICH GCP Art. 5.1].</p> <p>Depending on the agreement, the CTU shall plan the QA/QC on behalf of the customer and provide support for the formalisation of the processes in documented procedures.</p>
10.12.1 Monitoring Plan	<p>Monitoring shall be planned in accordance with ICH GCP [Art. 5.18]. The extent and nature of monitoring depends on the risk assessment of a study. A monitoring plan shall be developed under the sponsor's responsibility by taking into account the overall principles of the data management plan:</p> <ul style="list-style-type: none">• The risks regarding methodology, data quality and safety of the subjects should be taken into account.• The frequency and number of visits should be defined, as well as the tasks to be performed during initiation visits, interim on-site and close-out visits.• On-site and centralised monitoring should be proposed, if applicable.• The data/variables to be monitored should be defined.• The amount of source data verification should be defined, and the handling of protocol violations should be detailed.
10.12.2 Audit Plan	<p>Audits shall be planned in accordance with ICH GCP [Art. 5.19]. An audit plan shall be developed in collaboration with the customer and should be determined by:</p> <ul style="list-style-type: none">• The level of risks to the study subjects• The relevance of the study to submissions to RA• The number of subjects in the study• The type and complexity of the study• Any identified problem(s)
10.12.3 Data Handling	<p>Quality control shall be planned for each stage of data handling in order to ensure reliability and correctness of the data [ICH GCP Art. 5.1.3].</p> <p>For details on electronic data handling refer to the SCTO Data Management Guidelines.</p>

**10.12.4
Record Access**

All study related sites, source data/documents and reports shall be accessible for QA/QC purposes, i.e. for study related monitoring, auditing, IEC reviews or regulatory inspections [ICH GCP Art. 5.1.2]. To this end, the following shall be planned:

- If not already specified in the protocol, a written agreement with the investigators/**institutions** should be prepared stating that direct access is granted for QA/QC purposes.
- Correspondingly, it should be verified that each subject consents to direct access to his original medical records for QA/QC purposes (in writing, preferably included in the informed consent process).

**10.13
Finalisation
of Contracts**

Contracts between the CTU and suppliers/subcontractors shall be finalised.

**10.14
Submission to
Independent Ethics
Committees and
Regulatory Authorities**

In collaboration with or on behalf of the customer, the submission dossiers for IEC and RA, if applicable, shall be prepared as specified on the respective websites.

- The regulatory status of the study should be defined.
- A documented procedure should be prepared for the submission of the study documentation to the IEC and RA, if applicable.
- The distribution and possible delegation of tasks for the regulatory procedures should be defined.
- The timelines should be planned (IEC meeting dates may be found on the Swissethics website).
- The submission dossier should be compiled and submitted. It should be ensured that the current versions of the relevant forms as published on the respective websites are used.
- For international studies it should be checked, if submission to the local RA is required.
- A follow-up procedure of the submission of dossiers should be in place and should be tracked, if applicable.
- All documentation of correspondence has to be filed.

**10.15
Independent Data
Monitoring Committee/
Data Safety
Monitoring Board**

Based on the study's safety risk assessment, an Independent Data Monitoring Committee (IDMC), Data Safety Monitoring Board (DSMB) or other steering committee (clinical advisory board, peer review committee, safety board) shall be established to assess all safety aspects, the progress of the study with respect to e.g. safety data, critical efficacy endpoints, etc. [ICH GCP Art. 5.5.2].

- Prospective members should be contacted for proposal and validation of their involvement in the committee.
- Members should be independent of the study and (if applicable) of the financial backer of the study (e.g. company, foundation, etc.).
- At least one member should be a statistician. Clinicians knowledgeable about the disease indication should be represented, as well as clinicians knowledgeable in the fields of any major suspected safety effects (e.g. nephrology, cardiology, etc.).
- The role, membership and operating procedures for the committee should be defined and formalised, preferably in a charter or in a contract.
- The IDMC/DSMB should have written operating procedures and maintain written records of their meetings.

11 Project Set-Up Phase

The set up phase begins on the date of obtaining the ethical and regulatory approvals/authorisation and ends when the sponsor opens the study for accrual.

The objective of this phase is to set up the study sites and to start the project as soon as possible.

11.1 Project Management

Project timelines, budget and resources shall be continually monitored and adapted, if necessary. Development of documents should be monitored and assistance provided, if applicable.

11.2 Study Registration

The registration of all interventional studies is not yet a legal, but a scientific, ethical and moral responsibility.

- Prior to recruitment of the first subject, the clinical study project should be entered into an appropriate national or international publicly accessible study registry and/or the database of the superordinate organisation, if applicable.
- Thereafter, the attributed study identification number should be used as the unique identifier for all references to the study.
- A process and a responsible person for regular updates of the registry should be defined.

11.3 Logistics

Production, storage and allocation of the IMPs/MedDev, as well as any other study material provided to the study sites should comply with ICH GCP and **good manufacturing practice (GMP)** requirements.

- IMPs/MedDev should be produced according to GMP guidelines.
- The qualified person should release the IMP with a certificate confirming GMP conformity.
- Only after release by the sponsor, the IMPs/MedDev may be prepared and allocated to the study site(s) as previously defined in the development phase (see Chapter 10.8, Logistic Processes) or in the study protocol. The preparation and allocation processes should be documented (including temperature control, if necessary).
- Storage modalities at the site(s) should be defined, e.g. temperature control, etc.
- Access restrictions to storage facilities should be defined.
- A process for the transportation from storage facilities to the subjects should be defined according to the requirements of the protocol.
- A documented drug accountability procedure should be specified.
- A procedure for unused and/or expired products should be described.
- Destruction of study drug after study completion should be defined.

11.4 Essential Documents

The **trial master file (TMF)** and the **investigator site file (ISF)** shall be prepared in compliance with ICH GCP requirements [Chapter 8].

- All study relevant documents accrued up to this point are to be stored in the respective files [ICH CGP Art. 8.2].
- Documented procedures as well as checklists and templates for the compilation of the TMF and the ISF should be available.
- The administrative and regulatory prerequisites should be checked, especially the provision of **essential documents** by the sponsor as defined by ICH GCP.
- The essential documents needed by the sponsor for the conduct of the study should be compiled in the TMF.
- The essential documents needed by the investigator for the conduct of the study should be compiled in the ISF.
- The archiving process should be defined.

11.5
Site Initiation Visit

If the CTU acts as a CRO or monitor for the entire duration of a clinical study, an initiation visit shall be organised at each study centre for all employees involved in the study. This visit should be performed according to ICH GCP and the SOPs of the CTU and/or the sponsor.

- All employees involved in the study at a centre should be invited to a meeting and all responsibilities should be explained to the site staff in detail and documented in the authorization form.
- Any necessary documents/samples (e.g. lab kit, IMP) should be prepared for the training of all involved staff at the meeting.
- A presentation should be given covering all the basic aspects of the study, e.g. scientific, methodological, regulatory, ethical, safety and practical procedures, communication channels, and responsibilities.
- Study specific training should be provided, e.g. on the protocol, study specific SOPs, CRF completion, subject information sheets/informed consent forms, etc.
- The on-site availability of all study related equipment and products, including documentation, should be verified.
- The storage modalities and facilities for IMP/MedDev and biological samples should be checked.
- Responsibilities for and access rights to IMP/MedDev should be explained to all employees.
- Laboratory information and documentation should be checked for completeness.
- The ISF should be checked and completed, if applicable.
- The attendance of all study team members should be recorded, including their function in the study.
- After the visit, a visit report should be prepared, signed by the **principal investigator (PI)** and the monitor, and distributed to the site and to the sponsor.
- The monitor should send a follow-up letter to the site. Detected action items and a summary of the feasibility of the study at the site should be presented.

11.6
Data Management

Please refer to the SCTO Data Management Guidelines.

12 Conduct Phase

The conduct phase begins with subject recruitment and ends on the date of the database lock.

The objective of this phase is to conduct the study in compliance with the current protocol/amendments, with GCP and the applicable regulatory requirements, based on the previously developed project plans, the defined processes and established documented procedures.

12.1

Project Management

The CTU shall ensure the project management on behalf of the customer as defined and documented in a contract/service level agreement.

The project team shall ensure the coordination among all employees as well as qualitative and quantitative monitoring of the project. In multi-centre studies, a harmonisation of the clinical investigations among study centres should be prioritised.

- A list of the members of the project team should be created and kept updated, e.g. in a responsibility log.
- The information channels between team members and employees should be established and maintained, e.g. in a communication plan.
- Project timelines and project budget should be continually monitored and, if applicable, adapted and updated in agreement with the sponsor. Any substantial adaptation should be documented in an amended contract/SLA.
- Training (general and study specific) of new project team members should be ensured and documented.
- The project manager should conduct regular assessments of the project development, and appropriate corrective measures should be taken, if necessary.

12.2

Quality Assurance

Throughout the course of the study the previously planned QA/QC system (see Development Phase, Chapter 10.12, Quality Assurance) should be implemented and maintained. The CTU may take over the customer responsibilities, if specified and documented in the contract/SLA.

12.2.1

Study Monitoring

The conduct of the study in compliance with the current protocol/amendments, with GCP and the applicable regulatory requirements shall be monitored [ICH GCP Art. 5.18].

- Monitoring should be performed in accordance with the established monitoring plan (see Development Phase, Chapter 10.12.1, Monitoring Plan).
- A documented procedure in accordance with the requirements of ICH GCP [Art. 5.18.5] should be written and implemented for monitoring visits, including working instructions, templates for reports, follow up letters, etc.
- Monitors should be adequately trained and independent of the study. Their qualification should be documented [ICH GCP Art. 5.18.2].
- For off-site monitoring please refer to the SCTO Data Management Guidelines.

12.2.2

Auditing

Aside from and in addition to routine monitoring or QC functions, systematic, separate and independent examinations (audits) should be conducted on a risk based assessment to evaluate if all study related activities were performed according to the current protocol/amendments, GCP and the applicable regulatory requirements [ICH GCP Art. 5.19].

- The auditing of clinical studies should be performed according to the established audit plan (see Development Phase, Chapter 10.12.2, Audit Plan).
- Written procedures for auditing should be established and implemented. They should specify what to audit, how to audit, the frequency of audits, and the form and content of audit reports [ICH GCP Art. 5.19.3].

- Auditors should be adequately trained and independent of the study. Their qualification should be documented [ICH GCP Art. 5.19.2].
- The observations and findings of the auditors should be documented in an audit report.
- When required by the RA, a declaration of confirmation that an audit has taken place (**audit certificate**) should be provided.

12.2.3 Data Handling and Query Management

Quality control should be implemented to each stage of data handling to ensure reliability and correctness of the data [ICH GCP Art. 5.1.3].

- Data management personnel should perform regular data checks. If inconsistencies are detected, queries are sent to the monitor or directly to the investigator for clarification.
- The answer should be sent back (signed by the investigator and/or monitor for correctness), and the corrections should be implemented.
- Queries can be electronic or in paper form and become an integral part of the CRF.

For details on electronic data handling refer to the SCTO Data Management Guidelines.

12.3 Informed Consent Process

Every subject should give his/her written informed consent prior to being involved in any study specific activities [ICH GCP Art. 2.9, 4.8].

- The documented procedure of obtaining the informed consent of study subjects in compliance with the GCP requirements should be followed (see Development Phase, Chapter 10.6, Informed Consent Process).
- The consent process may be delegated to an appropriately qualified person. However, delegation and appropriate qualification should be documented and be in accordance with legal and ethical regulations.
- No undue influence on the study subject to participate or continue the study may be applied.

12.3.1 Subject Information

The study subject should be given information on all aspects of the study, both orally and in writing in a subject information leaflet/sheet.

- The written information should be in an uncomplicated language, avoiding medical terminology. Ideally, it should be provided in the first language of the subject. In general, for translation of written information certified translations are needed.
- The subject should not waive any of his rights.
- The templates provided on the websites of Swissethics and Swissmedic should be used.
- The subject information leaflet/sheet should be updated whenever new information relevant to the subjects becomes available (for details see below Chapter 12.7.4, Change Control).

12.3.2 Consent Form

By signing the consent form, the subject or his legally acceptable representative shall agree to the subject's participation in the study.

- Prior to agreeing to a study participation by signing the informed consent form, the subject should be allowed an ample period of time for reflection [ICH GCP Art. 4.8.7].
- The subject should be given the opportunity to ask questions, and a competent person should answer them.
- Both the person obtaining the consent (i.e. investigator or delegate) and the subject should personally sign and date the consent form.
- A signed copy of the subject information sheet and of the consent form should be given to the study subject; the original copy of the consent form should be kept in the ISF.
- Special procedures apply for studies performed under emergency situations and for studies performed with minors or persons in legal custody [HMG Art. 56].

12.4 Screening and Enrolment

An optimal and continuous enrolment of study subjects in accordance with the requirements of the protocol shall be aimed at.

- Details of all screened subjects should be captured in a screening log.
- Additionally, details of subjects who enter the study are kept in the study recruitment/enrolment log.
- Measures should be taken to optimise the compliance of subjects, especially to avoid losses to follow-up, and to ensure that the primary endpoint is reached.

12.5 Safety of Study Subjects

The physical and mental well being of study subjects shall always prevail over the interests of science [ICH GCP Art.2.3]. Depending on the agreement with the customer, the CTU ensures the following:

- The continual medical care should be ensured throughout the study. After study completion/termination it should be taken over by the treating general practitioner, if applicable.
- At the occurrence of safety signals, subjects should be informed, especially as it might affect subjects' consent.
- The investigator should ensure that the confidentiality of records that could identify subjects is maintained [ICH GCP Art.2.11].
- A medically qualified person, i.e. an investigator or a **sub-investigator** for the study, should take all study related medical decisions.
- Any (serious) AE should be documented and appropriate medical care should be provided – regardless if it occurs to the subject during the active treatment phase of the study or during the follow-up period as defined in the protocol.
- Any information on AEs/SAEs/SUSARs should be collected and reported according to the requirements of the protocol, the IEC and RA. For details see Chapter 12.6, Safety Reporting to IEC and RA, below.
- If SAEs occur in blinded studies and unblinding is deemed to be medically necessary, the defined unblinding procedure should be followed; the investigator should explain any unblinding to the sponsor and document it accordingly [ICH GCP Art.4.7].

12.6 Safety Reporting to Independent Ethics Committees and Regulatory Authorities

If agreed so with the customer in the contract/SLA, the CTU takes over the sponsor's responsibility of reporting SAEs.

Safety reporting shall be performed in accordance with the protocol and the regulatory requirements. Special requirements apply for studies with IMPs and for studies with Medical Devices.

12.6.1 Safety Reporting for Investigational Medicinal Products

The investigator should immediately report SAEs and SUSARs to the sponsor and the IEC [ICH GCP Art.4.11.1]. The processes for safety reporting, including causality assessment and determination of expectedness, should comply with the ICH E2A (Guideline for Clinical Safety Data Management: Definition and Standards for Expedited Reporting) as well as the respective specifications of the RA [VKlin Art.22,23] and the IEC regarding timelines and responsibilities.

Standardised documented procedures should be in place for the assessment, the collection and the reporting of any AEs and SAEs – whether or not related to the investigational product.

- All information on AEs should be collected by the investigator according to the protocol and reported to the sponsor via the CRFs.
- SAEs, which are not specifically exempted by the protocol, should be reported to the sponsor by the investigator within the time period specified by the sponsor in the protocol (usually within 24 hours of awareness) and regardless of the causality via a specific SAE reporting form.

- If necessary, an amendment to the protocol should be discussed in order to ensure the safety of the study subjects.

For details regarding reporting timeframes and accepted document formats refer to the websites of Swissethics and Swissmedic.

12.6.2 Reporting of Safety Signals

The sponsor should immediately report on current safety risks noted, taking both national and international data into account [VKlin Art. 20].

For details refer to the websites of Swissethics and Swissmedic.

12.6.3 Annual Safety Reports for IMPs

Throughout the whole duration of a study the investigator should normally annually submit written summaries of the study status to the IEC, and to the sponsor upon agreement [ICH GCP Art. 4.10]. The sponsor should submit to the RA all safety updates and periodic reports, as required by the regulatory requirements [ICH GCP Art. 5.17.3]. The national RA (i.e. Swissmedic) require the sponsor to compile and submit an annual safety report [VKlin Art. 23.4].

- The annual safety report is a summary of the current status of knowledge and should describe the identified and potential risks of active substances/medicinal products during clinical studies.
- The safety report should contain a precise, critical summary of the medicinal product's safety profile and new, relevant safety aspects and their effect on carrying out the clinical study. A list in table form showing **serious adverse drug reactions (SADR)** should also be appended, including detailed presentations of SUSAR from Switzerland and abroad, if applicable.
- The accompanying letter provided with the annual safety report should contain a short summary of the status of the clinical study in Switzerland (number of centres open/closed, number of subjects recruited/recruitment closed, and number of SAE/SUSAR).
- The sponsor should keep a list of all AEs reported by the investigators according to the protocol. This list should be provided to the RA (i.e. Swissmedic) upon request.

For details and templates refer to the websites of Swissmedic and Swissethics.

12.6.4 Safety Reporting for Medical Devices

For studies with medical devices (MedDev), severe incidents and health hazards as well as corrective measures should be reported to the RA and IEC [VKlin Art. 20, 24].

- Corrective measures considered important for the protection of the health and safety of the study subjects can and should be taken immediately by the sponsor and the investigators. The IEC and RA should be immediately informed in such cases.
- All severe incidents that occur in Switzerland and that are device related, or possibly device related, should be reported to both the responsible IEC and RA.
- The initial report should be submitted within defined timeframes, a more detailed report can be sent later on. There is no exception to this duty and there is no differentiation between expected and unexpected events.
- Severe incidents that occur in foreign countries, other events or issues including non-compliance of investigators should be notified immediately to IEC and to RA, if they lead to a re-evaluation of subject safety, could pose health hazards, or compromise the rights of study subjects in Switzerland.

For details and templates refer to the websites of Swissmedic and Swissethics.

12.6.5 Annual Safety Reports for Medical Devices

A report detailing the safety of the study subjects should be sent in once per year for the entire duration of the study [VKlin Art. 24.2]. The report should provide a complete overview and include the following elements:

- A list of all severe incidents that have occurred, including those that have occurred outside of Switzerland and/or in other studies performed with the investigational device.
- A summary of these events, an analysis of their clinical relevance and acceptability, and the sponsor's conclusion regarding the safety of the subjects.
- Any risk-reducing measures taken or planned.

For details refer to the websites of Swissmedic and Swissethics.

12.7 Change Control Process

The CTU shall ensure that any changes implemented during the course of a study are documented and reported to the RA and IEC, as required and appropriate.

12.7.1 Protocol Amendments

Any deviation from, or changes to the protocol should be submitted to the sponsor and the IEC before being implemented, except in case of a safety amendment due to immediate hazards or for changes involving only logistical or administrative aspects [VKlin Art. 19, ICH GCP Art. 4.5.2].

- Any planned changes to the procedures described in the protocol should be formalised in a version controlled **protocol amendment**.
- The amendment should be provided to all participating investigators for submission to the relevant IEC.
- The amendment should be submitted to the IEC and to the RA, if applicable.
- The respective changes are effective and can be implemented in the study only after approval of the amendment by the IEC and RA, if applicable.
- If the changes in the protocol affect the CRFs, those should be adapted as well.
- If the changes in the protocol entail changes to the subject information and informed consent form, those need to be adapted, too (see below Chapter 12.7.4, Informed Consent).

12.7.2 Protocol Deviations

Any deviation from the approved protocol should be documented and explained by the investigator or a person designated by the investigator [ICH GCP Art. 4.5.3].

- Documents concerning protocol deviations should be filed in the ISF.
- The sponsor and, if applicable, the IEC and the RA should be informed.

12.7.3 Advertisements

The availability of new important information about the product under investigation and/or protocol amendments may trigger a revision of advertisements for subject recruitment.

- If any advertisements (e.g. newspaper ads, posters, etc.) for subject recruitment are updated, a re-approval from the IEC and the RA, if applicable, is required.

12.7.4 Informed Consent

The availability of new important information about the product under investigation and/or protocol amendments may trigger a revision of the subject information sheet and/or informed consent form. If the changes might be relevant to the subject's willingness to participate in the study, he should be provided with the new information (ICH GCP Art. 4.8.2).

- The consent forms and subject information sheets should be updated (strictly respecting version control) and submitted for approval to the IEC and, if necessary, to the RA.

- All enrolled subjects should be provided with the new information, but not before the updated documents are approved by the IEC and the RA (i.e. Swissmedic), if applicable, except in case of important safety issues.
- The procedures for obtaining written informed consent should be repeated (see Conduct Phase, Chapter 12.3, Informed Consent Process).

12.7.5 **Case Report Form** **Management**

Any change or correction to a CRF should be version controlled and, if applicable, submitted for approval to RA and/or IEC.

For details refer to the SCTO Data Management Guidelines.

12.7.6 **Interim Analyses**

Interim analyses should be performed as planned in the protocol or earlier, if required by an independent data management board or data management committee.

12.8 **Study End**

The administrative and regulatory closure of centres shall be done after the last visit of the last subject (Last Patient Last Visit) and after data base lock.

- All essential documents as defined in ICH GCP [Art. 8.4] should be filed in the ISF and in the TMF.
- All queries should be resolved, the source data verification should be completed, a medical review should be performed, and the data should be archived.
- The database should be locked for final analysis. For details refer to the SCTO Data Management Guidelines.
- The monitor should perform a site close-out visit.

13 Completion Phase

The completion phase begins once the database is locked and ends when the appropriate data analysis is performed, the results are published, and the study portfolio is archived.

The objective of this phase is to finalise the clinical study project after the termination of the study. This includes analysing, evaluating and publishing the data, as well as the reporting to the IEC and the RA, if applicable. The project is considered closed when the data and documents are destroyed after the legally required period of archiving.

13.1 Data Analyses and Statistics

If delegated to the CTU, the study analyses shall be carried out in accordance with a statistical analysis plan (SAP) on behalf of the customer.

- The analysis should be carried out based on a locked database by a competent person using validated software packages and/or programmes.
- The steps should be tracked and deviations from the SAP should be explained.
- A quality control of the main criterion of the analysis should be conducted.
- The study statistician should prepare a statistical analysis report with detailed results of the analysis. This report should be transmitted to the investigator for information and to the sponsor for interpretation.

For details refer to the SCTO Data Management Guidelines.

13.2 Clinical Study Report

In accordance with ICH GCP [Art. 5.22], every clinical study shall be reported to the RA, as required by the applicable regulatory requirements. The final **clinical study report (CSR)** should report the results of the study in a clear, complete and objective way. The CTU may provide support in reporting the results as specified in the contract/SLA with the customer.

- Ideally, for writing CSRs the ICH E3 Guideline should be followed, which gives detailed guidance on the structure and content of CSRs. The guideline is intended to assist sponsors/sponsor investigators in the development of a report that is complete, free from ambiguity, well organised and easy to review.
- The CSR as described in ICH E3 is mandatory for pivotal studies, and suitable for the reporting of an individual study of any therapeutic, prophylactic or diagnostic agent conducted in study subjects. In certain cases abbreviated reports may be acceptable, e.g. for uncontrolled studies or other studies not designed to establish efficacy.
- Once validated by the sponsor, the report should be distributed to investigators, relevant RA, and IEC at their request.

13.3 Information of Independent Ethics Committees and Regulatory Authorities

Completion or premature termination of studies should be notified to the responsible IEC and to RA (i.e. Swissmedic), if applicable, within given timeframes [HMG Art. 5 4.6, VKlin Art. 21].

The sponsor should inform RA (i.e. Swissmedic) of the end of the clinical study after the last visit of the last study subject at the last Swiss centre. Swissmedic also expects to be informed of the premature termination of a study at an individual centre, e.g. because of a lack of study subjects or for safety reasons [VKlin Art. 21].

- The sponsor should inform the RA (i.e. Swissmedic) and the investigator should inform the IEC within 90 days after the completion of the study.
- In the case of premature termination of a study, the delay is reduced to 15 days. The reasons for the premature termination and any consequences thereof should be clearly stated.

- The sponsor should submit a final study report to the RA (i.e. Swissmedic) within 6 months after completion or premature termination of the study. As a reference date for submitting the final report, the RA (i.e. Swissmedic) accepts the international date of the end of the study.

13.4 Information of Subjects

According to the **Declaration of Helsinki (DoH)** study subjects are entitled to be informed about the overall results of the study upon request. The CTU may provide support for the preparation of the communication material, if agreed with the customer.

- In the case of blinded studies, the study subjects should be informed of the treatment they received after the unblinding.
- If applicable, communication material accessible to and tailored for the understanding of study subjects should be produced. It should be written in an uncomplicated language, if possible avoiding medical terminology. Ideally, it should be provided in the first language of the subjects.
- The communication material should be provided to the investigator(s) for distribution to interested study subjects.

13.5 Archiving

Archiving processes for data and documents at the sponsor's premises, at the sites and at the CTU shall be planned as required by legal and regulatory requirements [ICH GCP Art. 4.9.5, 5.5.6, 5.5.7] and according to the provisions set forth in the contract/SLA.

13.5.1 Archiving of Data and Study Documents

- The management of paper and electronic filing should be defined in a documented procedure.
- The methods used to archive the study documents should ensure that the documents remain complete, legible and accessible throughout the required storage period.
- The documents filed for each study and their storage places should be listed.
- Access to archives should be limited to duly authorised persons.
- Sponsors and investigators should store the data for at least 10 years after the study end/premature termination [VKlin Art.25].
- After this period, the study documents and electronic data should be destructed. Destruction should be monitored and documented.

13.6 Publication

All clinical research data shall be documented and reported free of ambiguity and in a complete, adequate, accurate and transparent way, as required by the Declaration of Helsinki. The CTU shall ensure that international reporting standards are followed and provides assistance, if agreed with the customer.

13.6.1 Publication Policy

The CTU should ensure that the publication policy defined in the protocol or in a separate agreement is followed.

- Sponsors have the ethical obligation to publish the results of their research projects, regardless if they are positive, negative or inconclusive.
- Sponsors are accountable for the completeness and accuracy of their reports.
- Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication.

13.6.2 Publication Standards

Established publication standards for ethical reporting, such as e.g. those by the International Society for Medical Publication Professionals in the Good Publication Practice Guidelines, should be followed for publications in peer-reviewed journals and presentations at scientific congresses.

- The study type determines the established reporting standards that should be followed, such as CONSORT¹ for randomised controlled studies and STROBE² for observational studies.
- Articles and presentations should be complete, balanced and clear.
- Reference to the unique study identification number should be included in all articles and presentations on clinical research.
- Interpretation of results should be unbiased, scientific and relevant to the audience.
- Discussion of results should be unbiased and placed in the context of other relevant literature, and the evidence cited should be balanced.
- Limitations of the study design and methodology should be described.
- Studies with related findings should be cited, especially when previous results conflict with the results being reported.

13.6.3 Authorship/ Contributorship

The uniform requirements for manuscripts submitted to biomedical journals published by the ICMJE³ should be respected.

- Authorship credit should be based on substantial contributions to:
 1. Conception and design, acquisition of data, or analysis and interpretation of data
 2. Drafting the article or revising it critically for important intellectual content
 3. Final approval of the version to be published
- Contributors who do not meet all three requirements do not qualify for authorship. They should be listed in the section on Acknowledgments.
- The CTU should ensure that it is acknowledged in the publication of the study results.

13.6.4 Disclosure of Conflicts of Interest

All participants in the publication process should disclose all relationships that could be viewed as potential conflicts of interest, e.g. financial or personal relationships that might inappropriately influence (bias) their actions.

13.7 Project Management

The CTU shall perform the administrative closure of the project and an overall project assessment in order to identify improvement potential for future projects.

13.7.1 Debriefing

A debriefing meeting at the end of the study project should be organised.

- The debriefing meeting should involve the internal and the relevant external project partners.
- Discussion points may be e.g. positive and negative aspects of the collaboration, the lessons learned, impact assessment of the project, etc.

1 CONSORT Consolidated Standards of Reporting Trials

2 STROBE STrengthening the Reporting of OBServational studies in Epidemiology

3 ICMJE International Committee of Medical Journal Editors

13.7.2 Project Evaluation

The project leader should perform an overall assessment of the project. He should identify and evaluate the optimisation potential.

- A review of budgetary, logistic and administrative aspects should be conducted.
- Data on customer and partner satisfaction should be collected (questionnaires, complaints).
- The results of internal and external audits of the project should be analysed and respective corrective actions implemented.
- A final review of the key performance indicators, the non-conformities and corrective actions should be conducted.
- The assessment of the effectiveness of the corrective actions should be planned.

Literature

Laws and Regulations

- Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) 2000, SR 812.21
Loi fédérale sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPth) 2000, SR 812.21
- Verordnung über klinische Versuche mit Heilmitteln (VKlin) 2001, SR 812.214.2
Ordonnance sur les essais cliniques de produits thérapeutiques (OClin) 2001, SR 812.214.2
- Bundesgesetz über den Datenschutz (DSG), 1993, SR235.1
Loi fédérale du 19 juin 1992 sur la protection des données (LPD), 1993, SR235.1
- Verordnung über die Offenbarung des Berufsgeheimnisses im Bereich der medizinischen Forschung (VOGB) 1993, SR 235.154
Ordonnance concernant les autorisations de lever le secret professionnel en matière de recherche médicale (OALSP) 1993, SR 235.154
- Verordnung über die nationale Ethikkommission im Bereich der Humanmedizin (VNEK), 2000 SR 814.903
Ordonnance sur la Commission nationale d'éthique dans le domaine de la médecine humaine (OCNE) 2000, SR 814.903
- Eudralex Volume 4: The Rules Governing Medicinal Products in the European Union, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products

Guidelines and Recommendations

- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 1964
- ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 (R1), 1996
- ICH Harmonised Tripartite Guideline, Guideline for General Considerations for Clinical Trials E8, 1997
- ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A, 1994
- ICH Harmonised Tripartite Guideline Clinical Investigation of Medicinal Products in the Paediatric Population E11, 2000
- ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports, E3, 1995
- ICH Draft Consensus Guideline, Data Elements for Transmission of Individual Case Safety Reports, E2B (R3) Step 2, 2005
- ICH Implementation Working Group, Questions & Answers E2B (R5), 2005
- ICH Draft Consensus Report, Development Safety Update Report, E2F Step 2, 2008

Standards

- SN EN ISO 9000:2005: QMS Fundamentals and Vocabulary
- SN EN ISO 9001:2008: Quality Management Systems – Requirements Excellence Model – EFQM 2010

Webpages

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| www.ich.org | www.swissmedic.ch | www.icmje.org |
| www.wma.net | www.swissethics.ch | www.ismpp.org |
| www.emea.europa.eu | www.consort.org | www.efqm.org |
| www.admin.ch | www.strobe.com | www.iso.org |

Supporting Documents

- Quality Policy of the CTU Network / SCTO Glossary of Terms

Annex

Glossary

This glossary includes the abbreviations and definitions of terms frequently used in the Guidelines for Good Operational Practice. For a comprehensive glossary refer to the current version of the SCTO Glossary of Terms.

Wherever applicable, the terms and definitions are based on ICH GCP, legal and regulatory authorities (i.e. Swissmedic, Swissethics, etc.) or other internationally acknowledged organizations (**European Medicines Agency**, International Organization for Standardization, etc.) and referenced accordingly. Definitions, which are not referenced and comments included for information (*in italics*), were agreed upon and approved by the QA Working Group of the CTU Network.

Term	Abb.	Definition	Reference
Adverse Event	AE	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).	ICH E6, 1.2
Amendment/Protocol Amendment		A written description of a change(s) to or formal clarification of a protocol. <i>Comment: An amendment becomes an integral part of the protocol.</i>	ICH E6, 1.3, 1.45
Audit Certificate		A declaration of confirmation by the auditor that an audit has taken place.	ICH E6, 1.7
Case Report Form	CRF	A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.	ICH E6, 1.11
Clinical Study/ Clinical Trial		Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. <i>Comment: In current usage, the term “trial” often refers to randomized trials, whereas “study” refers to observational studies. However, in GCP usage they are synonymous. In the Matrices, the term study is generally used for all categories of investigations as defined above.</i>	ICH E6, 1.12

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Term	Abb.	Definition	Reference
Clinical Study Report/ Clinical Trial Report	CSR/CTR	A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).	ICH E6, 1.13
Clinical Trial Unit	CTU	Clinical Trial Units (CTUs) are organisations established for the conduct of clinical studies with staff specialised in clinical research. <i>Comment: In Switzerland, they are public organisations, initiated through a unique partnership between the Swiss National Science Foundation (SNSF), the universities and the (university) hospitals to develop and improve academic clinical research.</i>	
Competent Authorities	CA	Refer to Regulatory Authorities.	
Confidentiality		Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.	ICH E6, 1.16
Contract		A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract. The contract is the legally binding document outlining the services provided. <i>Comment: The concept of contract is defined in a generic sense in this International Standard. The word usage can be more specific in other ISO documents.</i>	ICH E6, 1.17 ISO 9000:2005, 3.3.8.
Contract Research Organisation	CRO	A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.	ICH E6, 1.20
Customer		Organisation or person that receives a product, e.g. consumer, client, end user, retailer, beneficiary and purchaser. <i>Comment: A customer can be internal or external to the organisation.</i>	ISO 9000:2005, 3.3.5
Declaration of Helsinki	DoH	World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects	www.wma.net
Documentation		All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms), that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.	ICH E6, 1.22

Term	Abb.	Definition	Reference
Documented Procedure		A procedure, which is established, documented, implemented and maintained. A single document may address one or several procedures. A documented procedure can be covered by more than one document.	ISO 9001:2008, 4.2.1
Essential Documents		Essential Documents are those documents, which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Any or all of the Essential Documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).	ICH E6, 8.1
European Medicines Agency	EMA	The European Medicines Agency (EMA) is a decentralized body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.	http://www.ema.europa.eu/ema
Good Clinical Practice	GCP	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.	ICH E6, 1.24
Good Manufacturing Practice	GMP	EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use. <i>Comment: For Manufacture of Investigational Medicinal Products Annex 13 is relevant</i>	Eudralex Vol 4
Heilmittelgesetz/ Loi sur les produits thérapeutiques	HMG/LPTh	Bundesgesetz vom 15. Dezember 2000 über Arzneimittel und Medizinprodukte Loi fédérale du 15 décembre 2000 sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPTh) <i>Comment: This law is a national legal requirement for Switzerland</i>	www.admin.ch
Independent Ethics Committee	IEC	An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.	ICH E6 1.27

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Term	Abb.	Definition	Reference
Informed Consent		A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.	ICH E6, 1.28
Institution		Any public or private entity or agency or medical or dental facility where clinical trials are conducted.	ICH E6, 1.30
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.	www.ich.org
International Organization for Standardization	ISO	ISO is the world's largest developer and publisher of International Standards. ISO is a network of the national standards institutes of 160 countries, one member per country, with a Central Secretariat in Geneva, Switzerland, that coordinates the system.	www.iso.org
Investigational (Medicinal) Product	I(M)P	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. <i>Comment: There is no difference between IP and IMP. GCP uses IP and the Directive 2001/20/EC, Article 2 (d) IMP as abbreviations. Both are included as both are common.</i>	ICH E6, 1.33 Directive 2001/20/EC Article 2 (d)
Investigational Medicinal Product Dossier	IMPD	The Investigational Medicinal Product Dossier is required for approval of clinical trials by the competent authorities in the EU. It should provide information on quality data, non-clinical pharmacology and toxicology data, clinical trial and previous human experience data, and overall risk and benefit assessments for the test product, reference product and placebo.	http://ec.europa.eu
Investigator		A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. <i>See also Principal Investigator, Sub-investigator.</i>	ICH E6, 1.34
Investigator Site File	ISF	<i>See Trial Master File</i>	

Term	Abb.	Definition	Reference
Investigator's Brochure	IB	A compilation of the clinical and nonclinical data on the investigational product(s), which is relevant to the study of the investigational product(s) in human subjects (see ICH GCP Chapter 7, Investigator's Brochure)	ICH E6, 1.36
Management		Coordinated activities to direct and control an organisation or a project	ISO 9000:2005, 3.2.6.
Management System	MS	System to establish policy and objectives and to achieve those objectives.	ISO 9000:2005, 3.2.2.
Medical Devices	Med Dev	Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings. Devices are to be used for the purpose of: <ul style="list-style-type: none"> • Diagnosis, prevention, monitoring, treatment or alleviation of disease. • Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap. • Investigation, replacement or modification of the anatomy or of a physiological process • Control of conception 	Directive 2007/47/EC
Monitor		The Monitor is appointed by the sponsor and verifies that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents, and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable legal and regulatory requirement(s).	ICH E6, 5.18
Organisation		Group of people and facilities with an arrangement of responsibilities, authorities and relationships, e.g. company, corporation, firm, enterprise, institution, charity, association, or parts or combination thereof. <i>Comment: In this document the term organisation refers to the CTU. If any other organisation is referred to, it is specified.</i>	ISO 9000:2005, 3.3.1
Principal Investigator	PI	If a trial is conducted by a team of individuals at the trial site, the investigator who is the responsible leader of the team may be called the principal investigator.	ICH E6, 1.34
Procedure		Specified way to carry out an activity or a process.	ISO 9000:2005, 3.4.5

Glossary

Term	Abb.	Definition	Reference
Process		Set of interrelated or interacting activities, which transforms inputs into outputs.	ISO 9000:2005, 3.4.1
Product		Result of a process.	ISO 9000:2005, 3.4.2
Project		Unique process, consisting of a set of coordinated and controlled activities with start and finish dates, undertaken to achieve an objective conforming to specific requirements, including the constraints of time, cost and resources.	ISO 9000:2005, 3.4.3
Protocol		A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.	ICH E6, 1.44
Quality Assurance	QA	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).	ICH E6, 1.46
Quality Control	QC	The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial related activities have been fulfilled.	ICH E6, 1.47
Quality Management	QM	Coordinated activities to direct and control an organisation with regard to quality. <i>Comment: Direction and control with regard to quality generally includes establishment of the quality policy and quality objectives, quality planning, quality control, quality assurance and quality improvement.</i>	ISO 9000:2005, 3.2.8
Quality Management System	QMS	Management system to direct and control an organisation with regard to quality.	ISO 9000:2005, 3.2.3
Regulatory Authorities	RA	Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see ICH E6, 1.29). These bodies are sometimes referred to as competent authorities.	ICH E6, 1.49

Term	Abb.	Definition	Reference
Serious Adverse Event (SAE)/ Serious Adverse Drug Reaction (SADR)	SAE/SADR	<p>Any untoward medical occurrence that at any dose:</p> <ul style="list-style-type: none"> ● results in death, ● is life threatening, ● requires inpatient hospitalisation or prolongation of existing hospitalisation, ● results in persistent or significant disability/incapacity, or ● is a congenital anomaly/birth defect. <p>In addition, important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.</p> <p><i>Comment: See also ICH E2A</i></p>	ICH E6, 1.50
Service Level Agreement	SLA	<p>In contrast to a contract, an SLA would focus only on the performance metrics and service quality agreed to by both parties, and may be used as a measurement tool as part of the contract.</p> <p><i>Comment: The rationale for having a *separate* SLA document is that the SLA can be revised without having to revise the contract. The contract can just refer to the agreed SLA. The contract might then last for 2 years but the SLA may be reviewed quarterly, for example. This reduces the administrative burden of reviewing the contract too frequently.</i></p>	
Source Data		<p>All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).</p>	ICH E6, 1.51
Source Documents		<p>Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medico technical departments involved in the clinical trial).</p>	ICH E6, 1.52
Sub-investigator		<p>Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial related procedures and/or to make important trial related decisions (e.g. associates, residents, research fellows). See also Investigator.</p>	ICH E6, 1.56

Glossary

Term	Abb.	Definition	Reference
Sponsor		An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.	ICH E6, 1.53
Sponsor-Investigator		An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.	ICH E6, 1.54
Standard Operating Procedure(s)	SOP	Detailed, written instructions to achieve uniformity of the performance of a specific function.	ICH E6, 1.55
Subject/ Study (Trial) Subject		An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.	ICH E6, 1.57
Supplier		Organisation or person that provides a product, e.g. producer, distributor, retailer or vendor of a product, or provider of a service or information.	ISO 9000:2005, 3.3.6
Suspected Unexpected Serious Adverse (Drug) Reaction	SUSA(D)R	SUSARs (SUSADRs) are Adverse Drug Reactions that are suspected to be both serious and unexpected. <i>Comment: See also SAE and Unexpected Adverse Drug Reaction</i>	
Swiss Clinical Trial Organisation	SCTO	The Swiss Clinical Trial Organisation (SCTO) is the central cooperative platform for patient-oriented, clinical research in Switzerland.	www.scto.ch
Swiss Group for Clinical Cancer Research	SAKK	The Swiss Group for Clinical Cancer Research (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung, SAKK) is organised as a membership association. Based on a service agreement with the Swiss Confederation, SAKK is a decentralised, academic research institute conducting trials at all major Swiss hospitals and abroad. The SAKK is a non-profit organisation that investigates the efficacy and tolerability of new cancer therapies and further develops existing tumour treatments.	www.sakk.ch
Swiss National Science Foundation	SNSF	The Swiss National Science Foundation (SNSF) is the most important Swiss agency funding scientific research. It supports, as mandated by the Swiss Federal government, all disciplines, from philosophy and biology to the nano-sciences and medicine.	www.snf.ch

Term	Abb.	Definition	Reference
Top Management		<p>Person or group of people, who direct and control an organisation at the highest level.</p> <p><i>Comment: Depending on the CTUs, there are different terms for top management, e.g. executive board, executive manager, etc. Steering bodies may also have different names, e.g. technical committee, steering committee, management board or other terms.</i></p>	ISO 9000:2005, 3.2.7
Trial Master File/ Study Master File	TMF/SMF	A Trial Master File contains the minimal set of Essential Documents as defined in GCP Art. 8.2–8.4. It should be established at the beginning of the trial, both at the investigator/institution's site (Investigator Site File) and at the sponsor's office (Trial Master File/Study Master File).	ICH E6, 8
Unexpected Adverse Drug Reaction		An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).	ICH E6, 1.60
Verordnung über klinische Versuche mit Heilmitteln	VKlin/OClin	<p>Verordnung vom 17. Oktober 2001 über klinische Versuche mit Heilmitteln</p> <p>Ordonnance du 17 octobre 2001 sur les essais cliniques de produits thérapeutiques (OClin)</p> <p><i>Comment: This ordinance is a national legal requirement for Switzerland.</i></p>	www.admin.ch

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