swiss
clinical
trial
organisation

GUIDELINES FOR GOOD OPERATIONAL PRACTICE

Version

3.0

Guidelines for Good Operational Practice (GGOP)
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ABBREVIATIONS

AE	Adverse Event
BASEC	Business Administration System for Ethics Committees
CA	Competent Authority
CAPA	Corrective and Preventive Action
CEN	Comité Européen de Narmalisation (European Committee for Standardisation)
ClinO	Clinical Trials Ordinance[1]
CONSORT	Consolidated Standards of Reporting Trials
(p/e/i) CRF	(paper / electronic / interim) Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTU	Clinical Trial Unit
EC	Ethics Committee
FOPH	Federal Office of Public Health[2]
GCDMP	Good Clinical Data Management Practice
GCP	Good Clinical Practice
GGOP	Guidelines for Good Operational Practice
GMP	Good Manufacturing Practice
HRA	Human Research Act[3]
HRO	Human Research Ordinance[4]
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
I(M)P	Investigational (Medicinal) Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISO	International Organization for Standardization
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
QMS	Quality Management System
SA(D)R	Serious Adverse (Drug) Reaction
SAE	Serious Adverse Event
SAKK	Swiss Group for Clinical Cancer Research[5]
SAP	Statistical Analysis Plan
SCTO	Swiss Clinical Trial Organisation
SLA	Service Level Agreement
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TPA	Therapeutic Products Act[6]
WMA	World Medical Association

Note: For definitions of terms please refer to „Appendix 1 Glossary".

1 Verordnung über klinische Versuche (KlinV) / Ordonnance sur les essais cliniques (OClin)

2 Bundesamt für Gesundheit (BAG) / Office fédéral de la santé publique (OFSP)

3 Humanforschungsgesetz (HFG) / Loi relative à la recherche sur l'être humain (LRH)

4 Humanforschungsverordnung (HFV) / Ordonnance relative à la recherche sur l'être humain (ORH)

5 Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung

6 Heilmittelgesetz (HMG) / Loi sur les produits thérapeutiques (LPTh)

INTRODUCTION

The CTU network is a distributed national infrastructure, established in 2007 to facilitate academic or patient-oriented **clinical research** in Switzerland. With a country-wide influence, it is made up of six local **Clinical Trial Units (CTUs)**, situated in Basel, Bern, Geneva, Lausanne, St.Gallen and Zurich.

Each of these six centres for clinical research is closely linked to the medical faculties of a Swiss university, either as part of a local university hospital or linked to the university. The largest Swiss cantonal hospital, St.Gallen (KSSG), is also a member of the CTU network and collaborates with other Swiss universities on particular projects.

Combining forces, the CTU network not only forms a well established and nationally coordinated structure. Most notably, it also serves as the largest provider of services and education in academic clinical research in Switzerland.

The common objective of the CTUs is to provide services to **customers** (definition see figure 1 Part I: Management of the Organisation) in an academic clinical research setting, while meeting legal and ethical requirements.

CTU services are diverse, and have a wide range of tasks:

- advise customers on the design and conduct of clinical research, including submissions to **Ethics Committees (EC)** and **Competent Authorities (CA)**
- provide customers with methodological and logistical support (e.g. sound biostatistic models, **participant** recruitment, technical support)
- conduct clinical research in collaboration with and on behalf of customers (e.g. coordination of multicentre studies)
- provide training (e.g. GCP; Swiss law and regulations)

The **Swiss Clinical Trial Organisation (SCTO)** is the umbrella **organisation** of the CTU network. The SCTO coordinates and facilitates the cooperation between the CTUs and furthermore is committed to making Switzerland a more attractive location for clinical research.

With the ultimate goal to achieve more at national level, platforms were set up. In these excellence centres experts from CTUs and partners work together to harmonise processes and set national standards. This includes strengthening Switzerland's international competitiveness and promoting the conduct of multicentre studies. Furthermore, the platforms serve as central contact partners for authorities and national and international stakeholders for all questions concerning clinical research..

The SCTO coordinates these platforms and liaises with potential alternative interest groups.

All CTUs have committed themselves to align their own CTU **management systems** in accordance with applicable national and international regulatory requirements, namely with the Guideline for **Good Clinical Practice** of the **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use** (**ICH GCP**[7]), with internationally acknowledged process-oriented standards for **Quality Management Systems (QMS)**, with information security management (ISO 27001[8]), and with the Guidelines for Good Clinical **Data Management (Good Clinical Data Management Practices, GCDMP**[9]).

Based on the above commitment, the SCTO developed, in conjunction with the CTU network, the **Guidelines for Good Operational Practice (GGOP)**.

7 ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), 09 November 2016

8 ISO 27001 Information Security Management- Specification With Guidance for Use

9 Good Clinical Data Management Practices, Society for Clinical Data Management, October 2013

SCOPE AND OBJECTIVES

The GGOP represent a framework of common standards for professional and operational practice. It applies to management activities, as well as to clinical research management at the individual CTUs.

As a common CTU network standard, we recommend that these guidelines are implemented at each site including associated network partners. It is, however, within the competence of each CTU to adopt these guidelines depending on the specific needs of the individual organisation.

The guidelines should not only serve to guarantee participant safety and a high quality standard, but also to ensure careful use of restricted academic budgets. This can be reached through the application of risk-based strategies as described under 2.6.

Generally, the GGOP give guidance to the CTU network on quality implementation. The document is structurally divided into two main parts, including appendices:

Part I describes the establishment and maintenance of a quality management system.

Part II describes the CTU services for the support for the implementation and maintenance of clinical research management.

The aims are as follows:

- harmonisation of operational activities, including common documents mainly for CTU staff, investigators, and **sponsors**
- provision of standardised services to researchers
- continuous improvement of quality aspects and performance processes

Appendices describe individual topics related to the main document and are attached separately.

Please note that definitions for important terms are initialy marked in **bold** and can be found in Appendix 1: Glossary.

REGULATORY FRAMEWORK

The GGOP of the CTU network are in accordance with applicable national[10] and international law, regulatory requirements, as well as ethical guidelines and regulations.

The current regulatory repositories provide a clear and defined framework for the conduct of clinical research with respect to participants' safety, as well as ethical principles and data quality. In addition, the QMS, which is implemented at the individual CTUs, is based on internationally recognised models, such as ISO 9001.

The **Federal Act on Human Research (HRA)** clearly differentiates between **"Clinical Trials"** under ClinO and non-clinical **"Research Projects"** under HRO. Depending on the research approach, either one of these ordinances apply. The GGOP address and discuss the regulatory framework covering both ordinances. Projects under the HRO are not bound as strictly to GCP Guidelines and established quality standards such as monitoring. However, the guidelines as suggested in this document guarantee for a high quality standard both in terms of project management and data quality/reliability. We therefore suggest that the GGOP should remain an important guideline also for research projects. In all events, any research involving human beings is equally bound to respect the **Declaration of Helsinki**.

To facilitate the reading and ordinance applicability, the following definitions apply:

- clinical research: encompasses both *clinical* trials (ClinO) & *research* projects (HRO)
- clinical trials: refer only to studies conducted according to ClinO
- research projects: refer only to studies conducted according to HRO

10 Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act) as well as Federal Act of 30 September 2011 on Research involving Human Beings (Human Research Act) and its ordinances of 20 September 2013

REVISION HISTORY AND UPDATE

If there are any major regulatory changes or evidence for improvement, the SCTO in collaboration with the CTUs and the associated network partners will update the main document, at the latest, however, two years after its publication. The appendices are reviewed, adjusted and replaced on a continuous basis and as deemed necessary.

Revision of Version 2.0:

- On 9 November 2016, the ICH Assembly adopted an important amendment (ICH E6 (R2)), replacing the previous version R1. The fundamental differences between the R1 and R2 version of the guidelines are in respect to sponsor/investigator responsibilities and risk-based monitoring. As of 1 May 2017, Annex I of the **Clinical Trials Ordinance** (ClinO) refers to the amended Guideline 'ICH E6 (R2)'.
- A new version of the European Standard ISO 9001:2015 was approved by the European Committee for Standardisation (CEN) on 14 September 2015, replacing the previous version ISO 9001:2008. The most noticeable change is its shift in focus, emphasising the importance of describing one's organisation in the context of a broader networking structure (such as the relationship with relevant stakeholders). Furthermore, another major focus is an increased emphasis on risk-based thinking.
- Review of the introductory part of the guidelines to reflect structural changes within the CTU network since the last review.
- Simplification of wording throughout the document was performed for better reading comprehension.

Since the last revision, the following developments have become of national importance and are therefore stated in this document. However, in line with the general nature of this guideline, only a brief outline and links to further reference is provided:

- General consent or Broad Consent for Research (BCR): the Human Research Act, HRA, enacted in early January 2014, allows under certain conditions to establish a BCR, through which a person may give his/her consent or the use of his/her data and biological material for future research. A harmonisation process led to the development and subsequent publication of a national template (swissethics: http://www.swissethics.ch/templates_e.html). At the time of the current revision, the Swiss Biobanking Platform (SBP) was developing guidelines to support the set up and appropriate use of the BCR in the Swiss institutions.

The development and growing importance of the use of biobanks in clinical research:

- WMA (World Medical Association) Declaration of Taipei on ethical considerations regarding health databases and biobanks (Adopted by the 53rd WMA General Assembly, Washington, DC, USA, October 2002 and revised by the 67th WMA General Assembly, Taipei, Taiwan, October 2016),
- Swiss Biobanking Platform (SBP): A national coordination platform for human and non-human biobanks, which aims to respond to the increasing requests from biomedical researchers regarding quality and the interconnectedness of biobanks for research purposes (http://www.swissbiobanking.ch/).

PART I

MANAGEMENT OF THE ORGANISATION

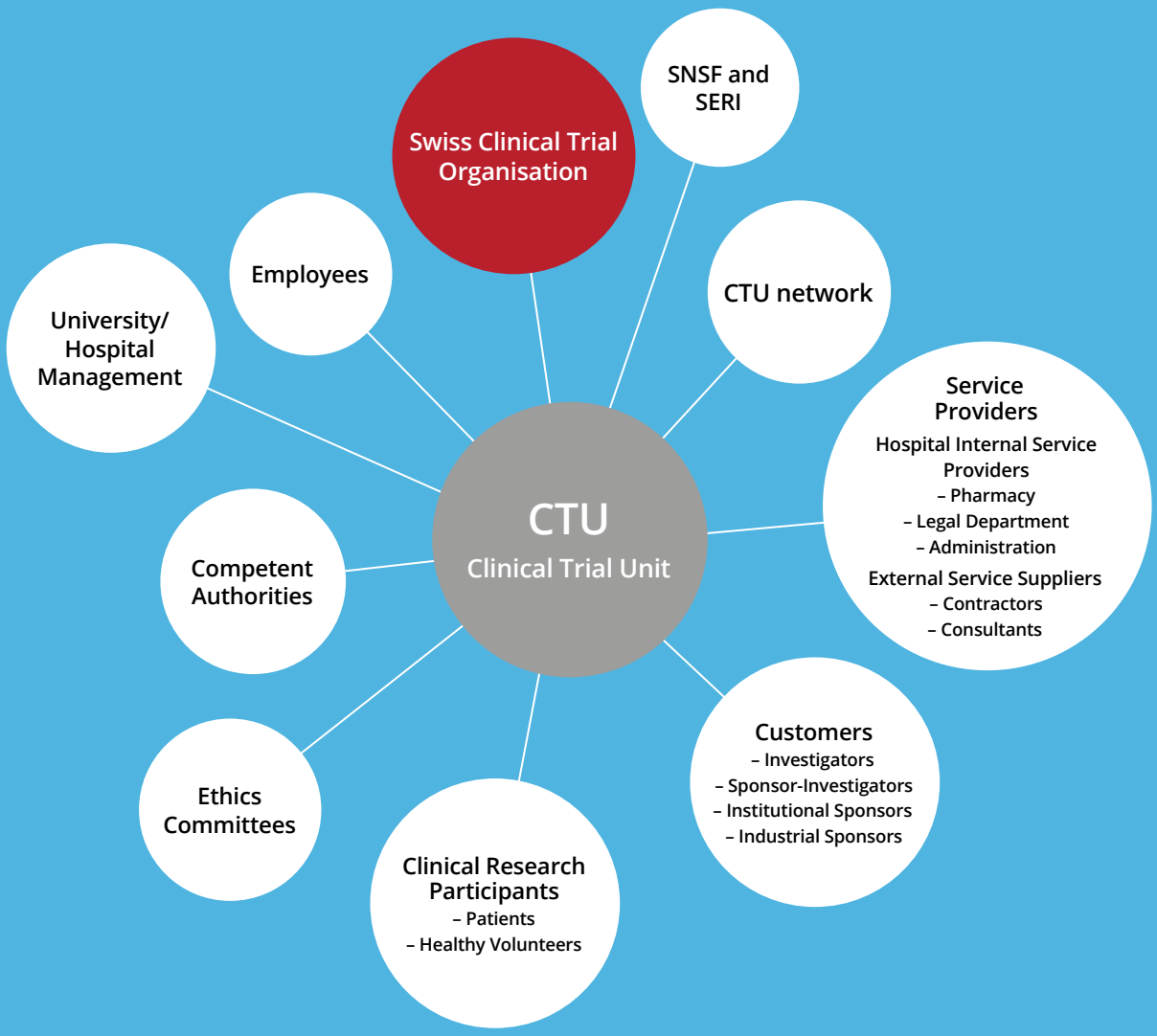

Figure 1: Typical Stakeholders of a CTU

In Switzerland there are six CTUs constituting a national network to support academic research in Switzerland. The CTU 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 required processes needed to support its customers in all aspects necessary for the conduct of clinical research: from the design to the publication of 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.

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 process-oriented and continually improves performance, while addressing the needs of all interested parties. Amongst other management disciplines, managing an organisation encompasses **Quality Management (QM)**.

Together with the QMS, the various parts of an organisation's management system might be integrated into a single management system using common elements. This can facilitate planning, allocation of resources, 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 given quality objectives, including stakeholder expectation and satisfaction. Generally, objectives complement other objectives of the organisation, such as those related to growth, funding, profitability, environment, and occupational health and safety.

1 STRATEGY AND MANAGEMENT RESPONSIBILITIES

Management strategy defines the context of an organisation and provides its focus. It ensures the durability and the development of activities. It anticipates the scientific and political developments while meeting the requirements of its stakeholders.

1.1 Strategy and Leadership

Top Management shall establish and maintain a management strategy aimed at fulfilling the mission and objectives of the organisation. Top Management defines and validates on an ongoing basis the strategic directions of the organisation.

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

- ensure that the quality policy and quality objectives are established for the QMS and are compatible with the context and strategic direction of the organisation
- ensure the integration of organisational QMS requirements to increase awareness, motivation and involvement of personnel and communicate the importance of an effective quality management
- promote the use of process approach and risk-based thinking, by addressing the risks and opportunities that can affect conformity of products and services, while taking accountability for an effective QMS
- ensure that legal, ethical and customer requirements are determined, understood and consistently met
- ensure that the resources needed for the QMS are available (facilities, infrastructure, financial and human resources)
- ensure that risks and opportunities that can influence conformity are determined and addressed
- in the event of planned changes, ensure that QMS achieves its intended results by performing an assessment of the effectiveness and of the suitability of the quality policy and quality objectives, of the resources, the processes, the specifications of the services and the implemented QMS
- engage, direct and support staff in their contribution to the effectiveness of the QMS
- promote improvement
- support other relevant management roles to demonstrate their leadership as it applies to their areas of responsibility.

1.2 Communication

Top management shall ensure that the information needed for the organisation to operate and to achieve its objectives is communicated in a timely manner, both internally and externally.

1.2.1 Internal Communication

Top management shall assign staff responsibility and authority regarding communication processes with respect to QMS efficiency (policy, requirements, objectives and results related to quality and the organisation).

- Tools should be identified and made available to staff to facilitate the flow of information within the organisation: e.g. team meetings, individual interviews, bulletin boards, internal newsletters, audio visual/electronic devices.
- The language of communication and documentation should be selected according to purpose and target audience.
- Frequency and type of communication tools should be defined.
- Transmission of information should be recorded.
- Communication channels between entities (units, departments) should be established.

1.2.2 External Communication

- Top management shall define a communication policy that ensures effective means of communication with partners, as well as the public. The following communication tools can be defined:
- Communication with stakeholders
- Establish suitable information channels
- Ensure strict customer **confidentiality**
- Communication plan regarding communication modalities with the public during emergency situations.
- As a general rule, all official communication should be documented.

2 QUALITY MANAGEMENT SYSTEM

The CTU, as an organisation, shall establish, document, implement, and maintain a process-oriented and risk-based QMS and continually improve its effectiveness. To this end, the QMS shall be based on current process-oriented international standards (e.g. ISO).

2.1 Quality Policy and Quality Objectives

Based on the strategy of the organisation, the CTU shall ensure that a quality policy and quality objectives are established, implemented and maintained. The legal, ethical and customer/service requirements should be taken into consideration.

2.1.1 Quality Policy

The quality policy should

- outline the general quality criteria and objectives appropriate to the purpose and the context of the organisation and support its strategic direction. These should be in compliance with the quality policy of the CTU network. The quality policy should act as a driver for continuous improvement, and thus commit to comply with QMS requirements.
- should take different process assessments and measurements into account.
- provide a framework for establishing and reviewing detailed quality objectives.
- be reviewed for applicability.
- be distributed, communicated and understood among staff members.

2.1.2 Quality Objectives

Quality objectives should be consistent with the quality policy of the organisation and shall:

- be established, communicated and planned.
- include relevant functions, levels and processes.
- be stated in a way that they are directly or indirectly measurable.
- ensure continuous improvement based on risk-based approach.

2.2 Quality Manager

CTU shall delegate the responsibility and authority over the QMS to an experienced person (e.g. quality manager, **quality assurance manager**). The quality manager should:

- preferably be independent from operational workflows
- report directly to the CTU head/director.
- be responsible for planning and supervising the QMS.
- be granted access to continuous training in order to maintain required skills and working knowledge.

The delegation of these requirements should be described in a document (e.g. job description).

2.3 Identification of Processes

Organisational processes and applications shall be defined and documented. They generally include **product** or service realisation, management responsibilities/activities, measurement, analysis and improvement.

- CTU processes should be compatible with the QMS of the superordinate organisation.
- Process in- and outputs should be identified and monitored on an ongoing basis including potentially subsequent corrective measures.
- Sequence and interactions of internal processes should be defined and documented.
- The availability of resources and information to support the operation and its monitoring should be ensured.
- Any outsourced process could affect the conformity of service requirements. The control over such processes should be ensured and defined in the QMS.

2.4 Documented Information

Generally, the QMS shall include **documented information** determined by the organisation as being necessary for the effectiveness of the QMS (ISO 9001:2015; 7.5.1.).

Based on the new ISO, documentation differentiates between **specifications** (3.8.5) and **records** (3.8.10). Please refer for further details to ISO 9001:2015.

The size and extent of the quality management documentation system varies depending on the organisation, on its size, the complexity of its activities, and the competence of its personnel. Documentation can take on any form and be of any type of medium.

When creating and updating documents, the following should be ensured:

- Identification and description (e.g. title, date, author, reference number)
- Format (e.g. language, software version, graphics) and media (e.g. paper, electronic)
- Review and approval processes.

2.5 Control of documented Information

For the overall life cycle of key documents procedures should be put in place, such as:

- guarantee of easy documentation identification by defining standard document identifiers and templates (e.g. document title page, standard footer with document reference/code, document versions etc.)
- approval prior to issue
- regular review, update, and re approval
- identification of changes and current revision status (version control, archived versions)
- availability and access of relevant document versions at points of use
- guarantee of legibility and easy identification
- guarantee the identification of internal and external documents
- prevent the unintended use of obsolete documents (e.g. password-protected access only by quality manager or designated personnel).
- establish documented procedures for the description identification, storage, access, protection, retrieval, and preservation of records.

Records should remain legible, identifiable and retrievable for a defined period of time.

If the procedures are based on processes from other, superordinate organisations, 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 of documents to ensure their compliance with applicable rules and regulations.

2.6 Risk Management

2.6.1 Management Review

In order to ensure the organisation's ongoing efficiency and quality performance, the CTU shall have a functional and current risk management policy in place. The following parameters should be taken into consideration during the review:

- the objectives of the organisation, including predefined key indicators
- changes within the structure of the organisation, including external stakeholders
- results of internal **audits**/self-assessments and external audits
- customer feedback and complaints
- service conformity assessments
- follow-up actions from previous management reviews and/or assessments
- opportunities for improvement
- the adequacy of resources

2.6.2 Risk Management Policy

The CTU shall have a risk management policy and consequent plans in place for the assessment and management of organisational risks. This policy should be defined by the CTU head/director and/or the quality manager and be transparent throughout the organisation. Supplementary international guidelines/ standards, such as ICH Q9[11] and/or ISO 31000[12] may be used as a basis for the risk policy implementation. Generally, the policy should include the following aspects:

- outline the general objectives as well as the resources made available to achieve them.

11 ICH Harmonised Tripartite Guideline. Quality Risk Management (Q9), 09 November 2005

12 ISO 31000:2009: Risk Management- Principles and Guidelines

- Responsibilities should be identified at appropriate levels.
- Applicable plans should be defined (e.g. general risk assessment plan, audit plan, risk-based maintenance plan, etc.)
- Measures should be taken to ensure effectiveness.
- Performance of risk-evaluation including external parameters, which could influence the organisation, the processes and/or the QMS.

3 SUPPORT: INFRASTRUCTURE AND ENVIRONMENT FOR THE OPERATION OF PROCESSES

The CTU shall ensure the suitability and security of the infrastructure and the environment for the operation of processes. These include 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 to achieve conformity of products and services.

- A responsible person should be identified to manage the CTU-relevant infrastructure. He/she is the contact person for the technical department of the superordinate organisation.
  - Periodic analysis should be performed as applicable
  - Preventive equipment maintenance should be planned and carried out as appropriate.
  - Maintenance **contracts** should be concluded with supplier's service departments.
  - Periodic equipment checks should be conducted as recommended by the supplier.
  - Maintenance checks should be planned.
  - Intervention records of equipment, premises, and materials should be kept throughout their lifetime.
  - Critical facilities should be identified based on a periodic risk analysis In addition a validated security system should be installed.
  - Critical equipment should be stored in facilities with restricted access.

3.2 Environment for the operation of processes

The CTU shall determine, provide and maintain the environment necessary for the operation of its processes and to achieve conformity of products and services. A suitable environment can entail a combination of human and physical factors, such as social (e.g. non-discriminatory), psychological (e.g. stress-reducing) and physical (e.g. hygiene) factors.

Hygiene standards and safety requirements for the environment for the operation of processes (facilities, equipment) should be defined.

- Ensure maintenance of the CTU premises and equipment, including the conduct periodic checks thereof.
- Guidelines on hygiene and safety descriptions in case of fire accidents should be in place, including training of all staff members.
- Staff should be familiar with existing hygiene and safety regulations through appropriate training.

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.

For details refer to the Appendix 2: Data Management Guidelines.

4 SUPPORT: HUMAN RESOURCES

CTU management shall determine and provide necessary personnel for the effective performance of all service-related activities, including the implementation, maintenance and continual improvement of a QMS and the operation and control of its processes. Responsibilities and authorities shall be defined and transparently communicated within the organisation.

4.1 Personnel

Personnel shall be competent[13] on the basis of appropriate education, training, skills, and experience.

- The necessary competence of personnel should be determined and documented (e.g. job descriptions). If applicable, internal and/or training should be provided and documents thereof duly filed.
- Personnel should be aware of the relevance and importance of their activities.
- Personnel should know how to contribute to the quality objectives.

4.2 Employment

Each staff member should have an individual employment contract in accordance with regulatory requirements.

- Each staff member should have a job description documenting the duties and responsibilities of his/her 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.
- The line manager should conduct an annual assessment interview with each staff member on the basis of the relevant job description. The modalities for conducting such an interview should be specified in writing.

4.3 Organisational Chart

Organisational chart(s) shall reflect the organisational structure including functions.

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

4.4 Staff Training and Integration

Professional training and continuous education shall be promoted and supported.

- A written procedure should describe the integration of new staff.
- An initial training plan should be established in order to ensure that new staff is adequately trained.
- Annual training goals should be defined for all employees.
- Training courses should be documented.

4.5 Interns/Volunteers

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, as well as the internship objectives.

13 See also ClinO Art. 6

5. SUPPORT: FINANCIAL MANAGEMENT

A financial management system shall allow assessment and planning of resources needed for the smooth operation of its activities.

- The CTU should be considered a full management unit, so that the expenses generated by the CTU can be clearly identified and thus can be covered by the superordinate organisation or the funding agency.
- The frequency of information exchange between the financial services of the CTU and the superordinate organisation should be defined.

6. SUPPORT: PURCHASING AND SERVICE PROVIDERS

The CTU shall have the resources needed for the proper implementation of clinical research, in compliance with the purchasing rules and regulations. If purchasing procedures are based on processes of superordinate organisations, they should be referenced as such in the documentation system.

6.1 Order Process

- Basic equipment and material (e.g. office material) should be ordered in accordance with the needs 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 formally documented.

6.2 Service Providers

- Service providers should be selected and assessed based on their impact on services and their ability to meet the specified needs.
- A formal process for the evaluation of service providers should be in place.
- Evaluations of service providers should be based on predefined evaluation criteria.
- Contracts with service providers, including audits may be drawn up for specific equipment/services (e.g. electronic data capturing software).

7. CHANGE MANAGEMENT

The CTU shall ensure that processes are defined for the assessment and communication, including changes which have a potential impact on the services provided by the organisation.

- A procedure should be in place for 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 identified and monitored.
- Continuous screening of applicable national and international laws and regulations should be performed.
- For every change, the quality manager should perform an impact assessment and a re-assessment of possible related risks.
- Depending on the relevant process and assessed impact of the change, the quality manager may set up a task force to update appropriate documents.
- All relevant personnel should be informed about any implemented changes.

8. MEASUREMENT, ANALYSIS AND IMPROVEMENT

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

8.1 Customer Satisfaction and Feedback from relevant interested Parties

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

- Any important feedback from customers and relevant interested parties should be collected and analysed (e.g. satisfaction surveys, complaints and claims made during projects).
- A survey analysis of positive points (criteria for satisfaction) allows an increase of knowledge.
- A survey analysis of average or negative points (criteria for dissatisfaction) enables the establishment of corrective actions for future projects.
- The needs of customers and relevant interested parties 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. **Auditors** should be independent of the audit process and shall not audit their own work.

- 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.
- All audit findings should be analysed and used to assess the effectiveness of the QMS and to identify opportunities for improvement.
- For any audit findings, Corrective and Preventive Actions (CAPAs) should be planned and implemented by the responsible line manager. Where applicable, the described procedure of change management should be applied.
- After implementation, the effectiveness of any CAPAs taken should be reviewed and, if applicable, further actions for improvement are taken.
- Records of audits and CAPAs should be maintained.

8.3 Measurement and Analysis of Processes and Services

A planned analysis of the effectiveness of the QMS shall ensure that processes and 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 feedback from relevant interested parties
  - conformity of services and products
  - characteristics and trends of services and products, including opportunities for preventive actions
  - service providers
- If applicable, improvement measures should be determined and implemented by the management.
- Where appropriate, the described procedure of change management should be applied.
- After implementation, the effectiveness of any improvement measure taken should be reviewed and if applicable, further actions for improvement are taken.
- Records of measurements and analysis of processes and services should be maintained.

8.4 Control of Non-Conformities

- Services and/or processes that do not comply with the requirements should be identified and controlled to prevent unintended use or delivery. A procedure for dealing with non-conformities should be in place, including the respective responsibilities.
- This procedure not only describes the actions to be taken to eliminate and prevent the detected non-conformities, but also describes actions in case customers detect 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.

- Processes should be formalised in documented procedures for:
  - Managing non-conformities (including customer complaints) and potential non-conformities
  - Determining 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

PART II

MANAGEMENT OF CLINICAL RESEARCH

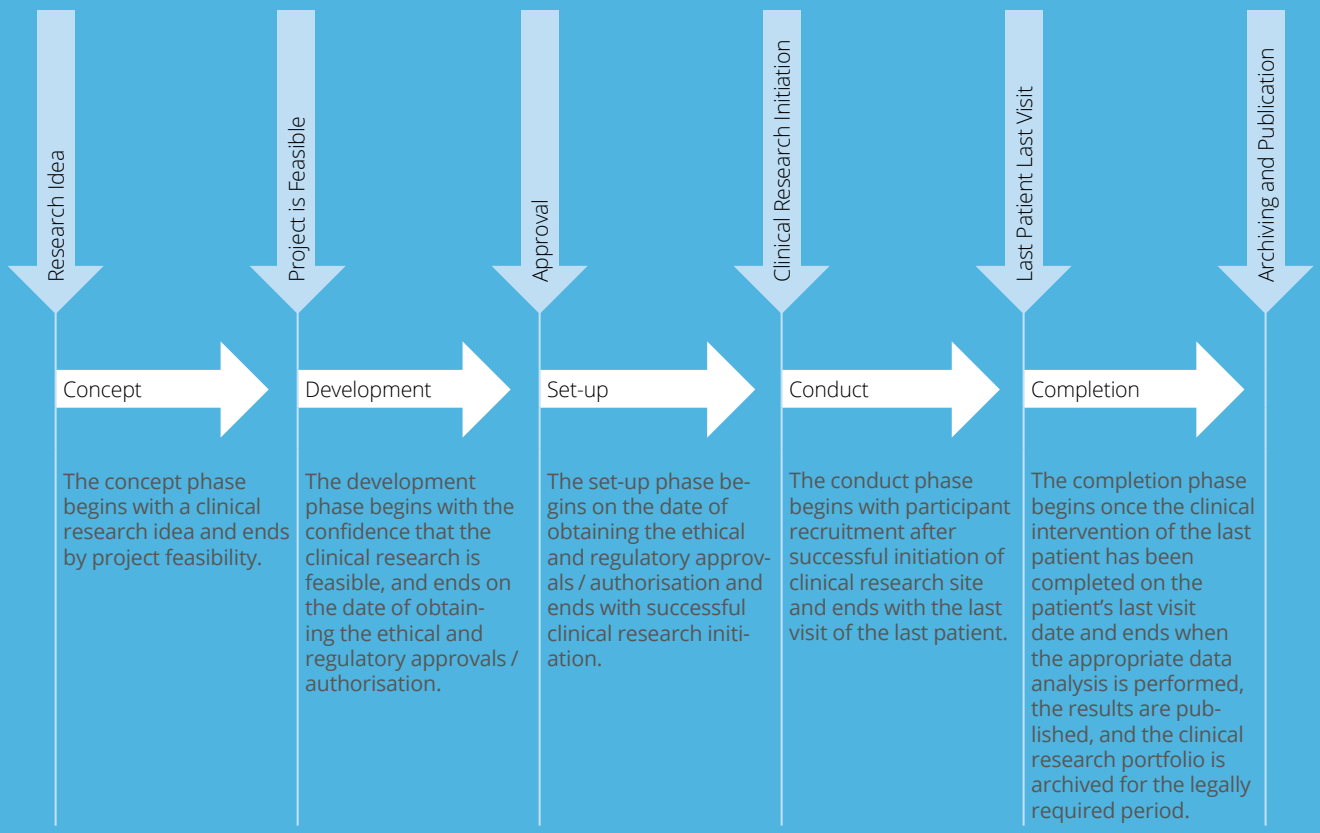

Figure 2: Phases of Clinical Research

Each CTU offers various services and performs a multitude of activities. However, a main service of CTUs is providing support for the planning and conduct of clinical trials and research projects.

As a service provider in clinical research the CTU can either assume the role of an academic **Contract Research Organisation (CRO)** by providing services related to the investigator's or **sponsor-investigator**'s activities and responsibilities[14] (such as in the context of regulatory affairs or on-site management) or assume the sponsor's[15] responsibilities (such as statistics, data management or monitoring activities).

Depending on the project role, the CTU performs activities and provides support, which is carried out in accordance with the applicable legal and regulatory requirements.

Services can be provided for the overall management of the clinical research project or only for specific subprocesses. According to ICH GCP, all tasks delegated by the sponsor should be specified in writing. Thus for each project, the CTU and the customer should define the scope including individual responsibilities in a contract and/or **Service Level Agreement (SLA)**. However, the ultimate responsibility for the quality of the clinical research and the integrity of the data remains with the sponsor.

Principally, customers can request CTU services at any point in time during the clinical research: starting with the initial planning followed by the conduct of the clinical research and closure activities. Requested services might encompass explicit activities, such as data analysis upon completion of the clinical research. As a result, individually specified services or a combination thereof may be requested.

The following sections of this document present a more detailed description of processes and requirements needed for the conduct and management of clinical research, which can be performed by the CTU. Sections are presented chronologically according to individual clinical research set-up phases (see Figure 2.)

14 Often, clinical research 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 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 Appendix 1: Glossary.

15 Refer to ClinO Art. 2 lit. c

9 CTU PROJECT DECISION

9.1 Capacity Evaluation

Based on a request, the CTU performs a capacity evaluation in order to evaluate availability of CTU resources. A designated CTU member should be responsible for the capacity evaluation and planning.

In the event the CTU is not able to provide support, the customer is to be informed as soon as possible. Upon acceptance, a corresponding contract and/or the SLA (Service Level Agreement) is prepared.

9.2 Contract and Service Level Agreement

Upon a mutual agreement between the CTU and the customer, services to be provided by the CTU including defined responsibilities are documented in a contract. In addition, for all paid services a quote detailing the planned service hours and fees will be submitted together with the corresponding contract. The CTU should decide whether the contract can be drawn up and signed directly with the customer, or if suppliers and/or other hospital internal departments are involved.

9.2.1 Overall Budget

An estimated overall budget for the clinical research should be established, not only taking financial resources into account, but also the required time and personnel. In addition, any collaboration with potential external partners should be included.

9.2.2 Contracts and Service Level Agreements

The necessary legal framework for the clinical research should be established in collaboration with the legal department of the hospital or any relevant third party.

Any responsibility delegated by the sponsor to e.g. a CRO or pharmaceutical company should be specified in writing, i.e. covered in a contract and/or a SLA [ICH GCP 5.2.2]. In addition,

- Processes on how to handle agreements and contracts, from development until approval, should be defined.
- Liability and other insurance issues should be clarified, including the nomination of a Swiss sponsor acting as a legal representative [ClinO Art. 2 lit. c], if applicable.
- Drafts of contracts with investigators, sites, CROs, pharmacies, service providers, etc. should be prepared.
- **Confidential Disclosure Agreements** should be drafted for investigators/suppliers.

9.2.3 Intellectual Property

- Ownership of **intellectual property** should be defined, including publication rights and patenting.

9.2.4 Conflict of Interest Policy

- The **Conflict of Interest** policy for investigators should be discussed with involved parties.
- Potential conflicts of interests for the CTUs should be assessed and made transparent.
- Draft documents for **Financial Disclosure** and/or investigator disclosure of interest documents should be drafted according to national laws.

10 CONCEPT PHASE

The concept phase begins with a clinical research idea and ends by project feasibility.

The objective of this phase is an evaluation of clinical research project feasibility: For the success of the project it is essential to check early on some elementary aspects, such as target group availability, potential collaborators and partners, required infrastructure, and required personnel.

If the feasibility assessment is delegated to the CTU, the CTU should designate a project responsible/contact person.

10.1 Project Evaluation

In order to evaluate the feasibility of a project, the sponsor should provide the CTU with as much information as possible, such as:

- project description or briefing (e.g. clinical research outline, including timeframe, task list)
- **protocol** or synopsis
- access to qualified personnel and available infrastructure

– **Investigator's Brochure** (IB) and Investigational Medicinal Product Dossier (IMPD)
– confidential disclosure agreement between customer and CTU

10.1.1 Scientific Aspects

The CTU may evaluate the project based on scientific aspects, such as:

– relevance, originality and innovation, and scientific quality of the project
– expected public health impact
– potential valorisation of results (e.g. publications, patents)
– methodological quality

10.1.2 Project Assessment

Depending on customer and requested support, a more detailed feasibility assessment can be performed.

Based on agreement and information provided, the CTU should evaluate the following aspects regarding clinical research management:

– Project feasibility regarding e.g. participant pool, analytical aspects, resources and equipment
– Expected timelines (customer expectations)
– Project-specific risk analysis regarding participant safety, e.g. radio actives, biological contamination
– Budget (expected costs), financing (e.g. funding, grants)
– Availability of the investigational product including placebo, if applicable
– Availability of project team (e.g. potential GCP-trained investigators, **study nurses**)
– Safety management, pharmacovigilance
– Data management and statistics, set-up of a professional databank according to regulatory requirements
– Appropriateness of facilities at clinical research site(s)
– Achievability of contracts and authorisations, including intellectual property
– Participant insurance[16],
– Investigator indemnification
– Legal permissions, e.g. for radio-actives
– Publication policy and agreement
– Conflict of interest policy
– Clinical trial registration
– Legal representation of sponsor (in case of foreign sponsor)

10.1.3 Conclusion

If the CTU comes to the conclusion that the project cannot be carried out as planned, the customer should be informed as soon as possible. The research team can evaluate alternative options for the design and conduct of the foreseen clinical research project to be resubmitted to the CTU for approval.

16 See also ClinO, Section 4: Liability and Coverage.

11 DEVELOPMENT PHASE

The development phase begins with the feasibility of the clinical research project and ends with ethical and regulatory approvals/authorisation.

The objective of this phase is to coordinate project resources and prepare documents for Ethics Committee (EC) and Competent Authorities (CA) submission (e.g. the Swiss Agency for Therapeutic Products (Swissmedic), and the Federal Office of Public Health (FOPH)).

11.1 Project Management

11.1.1 Project Team

An optimal management of the project should be guaranteed. In the event that the management of large projects is contracted, a multi-professional project team may be established including the nomination of a project manager.

The following points should be taken into consideration:

– The project team should have all skills necessary to manage the clinical research.
– Tasks and responsibilities within the project team should be clearly defined (task allocation list).
– Communication and reporting processes should be established.

– Delegation of responsibilities within the project group and with respect to the customer should be communicated to the project team members, including potential substitutes.
– 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 summarised in writing (e.g. project initiation document) and distributed to all involved parties.

11.1.2 Timelines

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

– Project timelines should be defined and captured in an overview.
– Individual timelines for all involved parties should be specified.

11.1.3 Human Resources

– The availability of appropriately skilled personnel should be ensured during the entire conduct of the clinical research.
– All personnel should be properly trained with respect to their assigned tasks, and training should be planned, as applicable.

11.1.4 Budget

Based on the estimated overall budget and in collaboration with the customer, a detailed financial project plan should be established, including:

– Estimated expected costs (based on quotes) from all involved (e.g. investigators' fees, database costs, CROs (e.g. for monitoring), laboratories, couriers, internal and external service providers, pharmacy, required apparatus etc.)
– A call for bids to be distributed and tracked regarding potential service providers
– Payment terms regarding participant allowance and reimbursements should be determined in relation to time, investment and constraints.
– Costs for insurance, import fees, etc. have to be clarified.
– Submission fees with EC and RA should be clarified, as applicable.
– The financial plan should be an integral part of the final customer contract.

11.2 Investigator's Brochure

The CTU may provide support for overall compilation or the improvement of the Investigator's Brochure (IB) and IMPD. 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 considered:

– The IB should comply with the requirements of ICH GCP 7.
– If an IB (and, if applicable, an IMPD) already exists, a current version (according to a one year rounding rule) should be available.

11.3 Protocol

The CTU may provide support for overall protocol development or improvement. Protocol templates and/or checklists as provided on the websites of swissethics[17] and/or Swissmedic[18] websites are to be used.

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

In particular, the following points should be checked and clarified in collaboration with the customer. As applicable, the protocol should:

– Have a clear hypothesis with primary and secondary endpoints.
– Use of methodological choices should be in accordance with scientific requirements.
– Define the population to be studied, inclusion/exclusion criteria, participant withdrawal criteria, randomisation method (e.g. web-based or using randomisation envelopes) and **blinding/un-blinding** processes should be defined.
– Determine assessment/evaluation criteria, examinations, and measuring methods.
– Describe administration and accountability of investigational products, intervention periods, follow-ups, including compliance.
– Define allowed/prohibited concomitant medication, rescue medication, and procedures for **Adverse Event (AE)** and **Serious Adverse Event (SAE)** reporting, including safety follow-up.
– Provide project-relevant literature and data.
– Categorise the clinical research project according to ClinO/ HRO.

17 www.swissethics.ch/templates_e.html
18 https://www.swissmedic.ch/swissmedic/de/home/suche.html#Protokoll%20vorlage

– Establish a data management and statistical analysis plan (including sample size calculation), including the timing of any planned **interim analyses**
– Check consistency of protocol with regards to **Case Report Forms (CRFs)** and **participant information**.

11.4 Data Management

If based on contract/SLA the data management will be performed by the CTU, the data managers have to be informed about the clinical research details. The database should be set up according to predetermined procedures (e.g. **Standard Operating Procedures (SOPs)**, regulatory requirements).

In general, the data managers are responsible for database set-up and **validation**, data entry, data correction processes, etc., however, depending on the set-up of the cross-functional project teams, some activities described herein may be performed by other members of the team and vice versa.

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 Appendix 2: Data Management Guidelines.

11.5 Case Report Forms

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

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

For details refer to the GCDMP guide and to Appendix 2: Data Management Guidelines.

11.6 Planning of Informed Consent Process

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

– Procedures describing how to inform clinical research participants and to obtain informed consent should be developed.
– Template documents and/or checklists should be used to draft participant information sheets and **informed consent forms**, e.g. as recommended on the website of swissethics.
– Special requirements apply for projects recruiting **vulnerable participants** such as children, adolescents, pregnant women, prisoners, participants lacking capacity, and emergency situations [HRA Art. 21 to 31, and ClinO Art. 15 to 17].

11.7 Selection of Clinical Research Sites

If not already defined by the customer, clinical research sites should be selected, ideally based on feasibility checks performed in an on-site pre-clinical research visit (selection visit). Alternatively, a standardised requirement list of criteria can be completed by telephone conference or mail correspondence.

The following aspects should be checked:

– Expertise within the clinical research field and motivation of investigators, including qualifications, education and experience in clinical research conduct and GCP.
– Availability of skilled staff, including back-up personnel.
– Estimation of realistic recruitment potential. Assistance in accelerating/improving recruitment can be offered to sites by preparing documents, website advertisements, etc.
– !Please note: overestimation of recruitment is a main reason for premature discontinuation of clinical trials.
– Availability of storage facilities for **Investigational Medicinal Products (IMPs)**/medical devices and biological samples should be checked. Access to these facilities should be restricted.
– Accessibility to specialised technical equipment/instruments, including a plan for regular quality checks should be prepared.
– Feasibility of planned timelines for all involved parties.
– Selection visits should be documented (selection visit report).

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

11.8 Logistic Processes

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

- The preparation (e.g. packaging, blinding, blistering), supply, distribution, storage and accountability of IMP/**medical devices**, i.e. from their production release to their final destruction, including labelling and temperature control as applicable
- Handling, storage and shipping of biological samples
- Processes with respect to time schedules, shipping instructions, temperature control, applicable shipping containers, etc.
- Access to additionally required material in collaboration with other departments, if applicable
- The planning of external support services regarding specialised technical equipment/instruments, such as electrocardiography
- Evaluate the need and availability of storage facilities
- The preparation of necessary **essential documents**

11.9 Evaluation of the Recruitment of Clinical Research Participants

The CTU can help to define participant recruitment processes, which are based on given eligibility criteria.

Processes include:

- Clarify participant screening, including the development of applicable screening document.
- Describe participant selection and the collaboration with medical networks.
- Formally assess recruitment potential according to eligibility criteria and based on on-site feasibility checks.
- Prepare participant adapted communication media (e.g. newspaper advertisements, leaflets, posters, internet sites) for EC submission.
- Identify quantitative and qualitative indicators for recruitment, monitoring (by site and for the overall recruitment across sites).

11.10 Safety Reporting

If agreed with the customer, the CTU can provide support regarding safety reporting for clinical research. According to the agreement, the following processes shall be planned:

- Details on task responsibilities and the delegation thereof
- Reporting of SAEs, and **Suspected Unexpected Serious Adverse Reactions (SUSARs)** to the sponsor, the EC and CA and other sites, including timelines for initial information and follow-up, as applicable
- Collection of non-serious AEs
- Annual safety reporting to EC and CA

Depending on the clinical research category, safety reporting varies significantly. For details on procedures and timelines refer to the websites of Swissmedic and swissethics as well as ClinO Art. 37 to 45, Art. 57, Art. 63, and ISO 14155[19].

11.11 Definition of Randomisation Process

Randomisation can be performed by the CTU. The randomisation process shall be set up as defined in the protocol. The following points should be considered:

- The randomisation procedures should be described.
- A randomisation list should be created that clearly identifies the participants by using project-specific identification codes. Participants' data should be anonymised on the CRF as per regulatory and legal requirements. See also HRO Art. 25 and 26.
- A person, preferably a statistician, who is otherwise independent of the clinical research, should produce the randomisation algorithm or list.
- The algorithm or list should be stored in a secure and confidential manner, not accessible to persons directly involved in the project. The list should be kept by (a) person(s) outside the project and accessible at all times for unblinding.
- Procedures for unblinding should be described, if not already defined in the protocol.
- Randomisation envelopes ("emergency envelopes") per site should be prepared, if applicable.
- An interactive voice response system or online randomisation functionality may be established, if applicable.

19 ISO 14155:2011: Clinical investigation of medical devices for human subjects (Good clinical practice)

11.12 Quality Assurance

- To ensure that clinical research is conducted and the data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements, a **Quality Assurance (QA)** and a **Quality Control (QC)** system with comprehensive SOPs should be implemented and maintained [ICH GCP 5.1].
- The CTU can assist in the set-up and planning of a QA/QC system needed for the implementation of a clinical research project.

11.12.1 Monitoring Plan

- Monitoring shall be planned in accordance with ICH GCP 5.18. The extent and nature of monitoring depends on the risk analysis of a project. A monitoring plan shall be developed under the sponsor's responsibility by taking into account the overall principles of the Data Management Plan.
- For details refer to the Appendix 3: Guidelines for Risk-Adapted Monitoring.

11.12.2 Audit Plan

Audits may be planned with the CTU in accordance with ICH GCP 5.19. An audit plan shall be developed in collaboration with the customer and should be determined by:

- the level of risks to the clinical research participants
- the relevance of the clinical research to submissions to CA
- the number of participants in the clinical research
- the type and complexity of the clinical research
- any identified problem(s)

11.12.3 Data Handling

- Quality control shall be planned for each stage of data handling in order to ensure reliability and correctness of the data [ICH GCP 5.1.3].
- For details on electronic data handling refer to Appendix 2: Data Management Guidelines.

11.12.4 Record Access

All clinical research related sites, **source data**/documents and reports should be accessible for QA/QC purposes, i.e. for trial-related monitoring, auditing, EC reviews or regulatory **inspections** [ICH GCP 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 participant consents to direct access to his original medical records for QA/QC purposes (in writing, preferably included in the informed consent process).

11.13 Submission to the Ethics Committee and Competent Authorities

In collaboration with or on behalf of the customer, the submission dossiers for EC and CA, as applicable, is prepared by the CTU. Submission entails:

- Procedure should be prepared for submission to the EC and CA, as applicable.
- Distribution, including delegation of tasks regarding regulatory procedures should be defined.
- Timelines should be planned.
- When compiling the submission dossier, one should ensure that the current versions of the relevant forms, as published on the respective websites, are used.
- For **multisite** clinical research, the submission is administrated by the lead EC. For further details see HRA Art. 47 (2), ClinO Art. 27, HRO Art. 17 as well as www.swissethics.ch.
- For international clinical research, the necessary submission to the local RA should be checked.
- Follow-up procedure of the submission should be in place and tracked, as applicable.
- All correspondence should be filed.

11.14 Independent Data Monitoring Committee / Data Safety Monitoring Board

Based on the clinical trial's safety risk analysis, 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 in order to monitor safety aspects and the progress of the clinical trial with respect to e.g. safety data, including critical efficacy endpoints [ICH GCP 5.5.2].

- Prospective members should be contacted for proposal and validation of their involvement in the committee.
- Members should be independent of the clinical trial and (if applicable) its financial backers (e.g. company, foundation).
- 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).
- The role, membership and operating procedures of 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.

12. PROJECT SET-UP PHASE

The set-up phase begins on the date of obtaining the ethical and regulatory approvals/authorisation and ends with clinical research initiation.

The objective of this phase is to set up the clinical research project at the site(s) and to start the project as soon as possible.

12.1 Project Management

- Project timelines, budget and resources must be continually monitored and adapted, including ongoing document development and tracking.

12.2 Clinical Trial Registration

The registration of all interventional clinical trials is a legal[20], scientific, ethical and moral responsibility.

- Prior to recruitment of the first participant[21], the clinical trial should be registered into
  - a primary registry recognised by the **World Health Organization (WHO)** (http://www.who.int/ictrp/network/primary/en/) or in the registry of the U.S. National Library of Medicine (www.register.clinicaltrials.gov), as well as into
  - the BASEC portal https://submissions.swissethics.ch/en/) which automatically feeds into the Swiss federal database Swiss National Clinical Trials Portal (SNCTP).
- Thereafter, the attributed clinical trial unique identification number is used for all future registry updates and correspondence.
- A person responsible for regular registry updates (at least once a year)[22] should be defined.

12.3 Logistics

Production, storage and allocation of IMPs/medical devices, as well as any other **clinical research** material provided to the site(s) should comply with ICH GCP and **Good Manufacturing Practice (GMP)** .

- IMPs/medical devices should be manufactured according to GMP guidelines and distributed to sites according to Good Distribution Practice (GDP) guidelines.
- Qualified personnel release the IMP with a certificate confirming GMP conformity.
- Only after having been released by the sponsor, may the IMPs/medical devices be prepared and allocated to the site(s) as previously defined in the development phase (see Chapter 11.8 Logistic Processes) or in the protocol.
- Preparation, allocation and storage modality processes should be defined and documented (including temperature control, if applicable).

20 Refer to ClinO Art. 64 to 67

21 Variation might be applicable for Phase I clinical trials, refer therefore to ClinO Art. 65 (2)

22 Refer to ClinO Art. 65 (3)

- Access rights to storage facilities should be defined.
- Based on protocol, a process describing transportation from storage facilities to participants should be defined.
- An IMP/medical device accountability procedure should be specified.
- Procedures to follow for unused and/or expired IMP/medical device products should be described, including their destruction upon trial completion.

12.4 Essential Documents

The **Trial Master File (TMF)** and the **Investigator Site File (ISF)** shall be prepared in compliance with ICH GCP requirements [ICH GCP 8].

- All clinical research relevant documents accrued should be stored in the respective files [ICH GCP 8.2].
- Where justified, essential trial documents may be supplemented or reduced based on their importance and or relevance to the trial.
- Storage and accessibility of the records should be evaluated for their suitability.
- An overview of record locations of all essential documents should be prepared by the sponsor and investigator and updated regularly till trial termination [ICH GCP 8.1].
- Checklists and templates for the compilation of the TMF and the ISF should be made available.
- Essential sponsor documents needed for the conduct of the clinical research should be compiled in the TMF.
- Essential investigator documents needed for the conduct of the clinical research should be compiled in the ISF.
- The investigator should have control over all essential documents and records generated before, during and after trial conduct (e.g. content of CRFs).
- When a copy is used to replace an original document, it should fulfil the requirements for certified copies [ICH GCP 1.63].
- An archiving process should be defined (See 14.5 Archiving). [ClinO art. 45; ICH GCP 8.1].

12.5 Site Initiation Visit

If the CTU acts as a CRO or monitor for the entire duration of a clinical trial, an initiation visit shall be organised at each clinical trial site for all staff members involved. The initiation visit is planned and performed according to ICH GCP and the CTU and/or the sponsor SOPs.

- All site staff involved in the clinical trial should be invited to attend the meeting.
- Responsibilities should be explained and captured in the delegation log.
- The principal investigator is responsible to supervise all delegated tasks and ensure the qualification and training of its delegates [ICH GCP 4.2.5]
- Training documents and any necessary documents/samples (e.g. lab kit, IMP) should be prepared for the training of all involved staff.
- A presentation should be given covering all the basic aspects of the clinical trial, e.g. scientific, methodological, regulatory, ethical, safety and practical procedures, communication channels, and responsibilities.
- Clinical trial specific training should be provided, e.g. protocol, clinical trial specific SOPs, CRF completion, participant information sheets/informed consent forms, etc.
- Availability of onsite clinical trial-related equipment and products, including documentation, should be verified.
- Storage modalities and facilities for IMP/medical devices and biological samples should be checked.
- Responsibility and access rights to IMP/medical devices should be explained.
- Laboratory information and documentation should be checked for completeness.
- The ISF should be checked and completed, if applicable.
- The attendance of all clinical trial team members should be recorded, including their function.
- After the visit, an initiation visit report should be prepared, signed by the **Principal Investigator** and the monitor, to be distributed to site(s) and sponsor.

12.6 Data Management

Please refer to Appendix 2: Data Management Guidelines.

13. CONDUCT PHASE

The conduct phase begins with participant recruitment upon initiation of the clinical research site and ends with the last visit by the last patient.

The objective of this phase is to conduct clinical research in compliance with current protocol/amendments, with GCP, applicable regulatory requirements, including additionally relevant procedures (e.g. SOPs, QM, processes, laboratory manuals, etc.)

13.1 Project Management

The CTU shall ensure on behalf of the customer the project management of the clinical research and as defined in a contract/SLA.

The CTU project team is responsible for the coordination among employees while performing ongoing, qualitative and quantitative project monitoring. In multisite clinical research, priority should be set on harmonisation among investigations at clinical research sites.

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

13.2 Quality Assurance

Throughout the course of the clinical research, the planned QA/QC system (see Chapter 11.12 Quality Assurance and chapter 5 of ICH GCP) should be implemented and maintained. Based on the contract/SLA, the CTU may take over this task.

13.2.1 Clinical Trial Monitoring

The conduct of the clinical trial shall be adequately monitored in compliance with the monitoring plan and relevant SOPs, the current protocol/amendments, with GCP and the applicable regulatory requirements. The sponsor determines the appropriate extent and nature of monitoring [ICH GCP 5.18.3].

- Monitoring should be performed in accordance with the established monitoring plan (see Appendix 3: Guidelines for Risk-Adapted Monitoring).
- For monitoring visits, procedures in accordance with the requirements of ICH GCP 5.18.5 should be implemented, including working instructions, report templates, follow-up letters, etc.
- Monitors should be adequately trained and independent of the clinical trial. Their qualifications should be documented [ICH GCP 5.18.2].

13.2.2 Auditing

Aside from and in addition to routine monitoring or additional QC functions, systematic, separate and independent examinations (audits) should be conducted on a risk-based assessment. It should be evaluated whether all clinical research-related activities were performed according to the current protocol/amendments, GCP, applicable regulatory requirements [ICH GCP 5.19] and other relevant documents (including SOPs, QM processes, biobank processes, contracts, etc.).

- The audit should be performed according to a defined audit plan (see Chapter 11.12.2 Audit Plan).
- Auditing procedures should be defined in a SOP. Specifications should be made to the audit scope, how to audit, audit frequency and the form and content of the **audit report** [ICH GCP 5.19.3].
- Auditors should be adequately trained and independent of the clinical research. Their qualification should be documented [ICH GCP 5.19.2].
- Audit observations and findings of the auditors are summarised in an audit report [ICH GCP 5.19.3].
- If applicable, a declaration or confirmation that an audit has taken place (**audit certificate**) should be provided.
- An additional audit reference is ISO 19011:2011: Guidelines for auditing management systems [23].

13.2.3 Data Handling and Query Management

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

23 ISO 19011:2011: Guidelines for auditing management systems

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 Appendix 2: Data Management Guidelines.

13.3 Informed Consent Process

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

- Compliance with the GCP requirements should be followed when obtaining informed consent of clinical research participants (see Chapter 11.6 Planning of Informed Consent Process).
- The consent process may be delegated to an appropriately qualified person, according to legal and ethical regulations.
- Research participants should not be subjected to any inappropriate influence regarding trial participation or continuation.

13.3.1 Participant Information

The clinical research participant should be given adequate information on all aspects of the clinical research, both orally and in writing, as appropriate.

- Participant information templates provided on the swissethics webpage[24] should be used.
- The written information should be in an uncomplicated language, avoiding medical terminology.
- Ideally, the information should be provided in the first language of the participant. The sponsor is responsible for the correct translation (in terms of form and content).
- Exemption to the written form can be granted based on physical or cognitive reasons, or if the participant cannot read or write. Nevertheless, proof of information given must be furnished (e.g. written confirmation by witnesses (ClinO Art. 8).
- In individual cases, information in written form may be waivered, if its implementation requires disproportionate effort, given the language skills of the participant. In this case an independent qualified translator should confirm the information given (ClinO Art. 8).
- The participant information sheet should be updated whenever new information relevant to the participants becomes available (for details see Chapter 13.7.4. Informed Consent Form)

13.3.2 Informed Consent Form (ICF)

By signing the ICF, the participant or his **legally acceptable representative** agrees to participate in the clinical research.

- Informed consent templates provided on the swissethics webpage should be used.
- Prior to agreeing, the participant should be granted ample time for reflection [ICH GCP 4.8.7].
- The participant should be given the opportunity to ask questions.
- Both the person obtaining the consent (i.e. investigator or delegate) and the participant should personally sign and date the consent form.
- A copy of the information sheet and the signed consent form should be handed out to the participant; the original consent form is filed in the ISF. As an alternative, two originals can be signed (like for contracts). One is given to the participant, the other one is filed in the ISF.
- Special informed consent procedures apply in emergency situations and for research performed with minors or persons in legal custody [HRA Art. 21 to 31, ClinO Art. 15].
- Exemption to the written form can be applied based on physical and cognitive reasons, or if the participant cannot read or write. Nevertheless, proof of consent given must be furnished (e.g. written confirmation by witnesses, recording of verbal consent (ClinO Art.8).
- In the event of participant revocation, anonymisation of its biological material and personal data should be undertaken once data evaluation has been completed (exemption to anonymisation see ClinO Art. 9 / HRO Art.10).

13.4 Screening and Enrolment

The aim should be to guarantee for an optimal and ongoing enrolment of clinical research participants in accordance with protocol requirements.

- Details on screened participants should be captured in a screening log.
- Participants who enter the clinical research are detailed in the clinical research recruitment/ enrolment log.
- In order to ensure that all primary endpoint(s) are reached, measures should be taken to optimise the participant and reduce losses to follow-up.

24 www.swissethics.ch/templates_e.html

13.5 Safety of Clinical Research Participants

The physical and mental **wellbeing** of clinical research participants shall always prevail over the interests of science [ICH GCP 2.3]. Depending on customer agreement, the CTU will assist project investigations in the following tasks:

- Ongoing medical care throughout the duration of the clinical research. Upon completion/termination, any required further medical intervention should be taken over by the treating general practitioner.
- Inform participants regarding the occurrence of **safety signals**, as it might affect their consent.
- Ensure confidentiality of records preventing participant identification [ICH GCP 2.11].
- A medically qualified person, i.e. an investigator or a **sub-investigator** for the clinical research, should take all related medical decisions.
- Any (serious) AE should be recorded and appropriate medical care should be provided – regardless if it occurs during the active intervention/research project phase or during the follow-up period.
- Any AEs/SAEs/SADRs/SUSARs should be collected and reported according to the protocol, EC and RA requirements. For details see Chapter 13.6 Safety Reporting to the Ethics Committees and Competent Authorities.
- If SAEs occur in a blinded clinical trial, a predefined un-blinding procedure should be followed; the investigator decides whether un-blinding is warranted, reports accordingly to the sponsor and documents it accordingly [ICH GCP 4.7]. In the event of a SUSAR, unblinding is always mandatory.

13.6 Safety Reporting to the Ethics Committees and Competent Authorities

Based on the contract/SLA, the CTU can assist the sponsor regarding his/her SAE reporting duties.

Safety reporting shall be followed according to the protocol and the ordinances of the Swiss law (ClinO and HRO). Reporting requirements to the EC and CA are adapted based on trial risk category.

13.6.1 Reporting of Safety Measures

In the event that immediate safety measures have to be implemented during the conduct of a clinical research, investigators must report undertaken measures to the EC and RA (if applicable), including the circumstances necessitating them.

Clinical Trials:

Reporting timelines to the EC (usually performed by the investigator):

- 7 days for medicinal products
- 2 days for medical devices

Reporting of safety measures to competent authorities (sponsor responsibility) (ClinO Art. 37):

- Required for all category B and C trials
- Reporting timelines as described for EC

Research projects:

Reporting of Serious Event (SE) (HRO Art. 21):

- The event must be reported to the EC within 7 days
- The research project must be put on hold
- The EC has 30 days to decide on whether the project should continue

For details refer to the websites of Swissmedic and swissethics.

13.6.2 Safety Reporting for Investigational Medicinal Products

Upon awareness, the investigator should immediately or within 24 hours report all SAEs and SUSARs to the sponsor.

- SAEs resulting in death are reported to the EC within 7 days [ClinO Art. 40].
- SUSARs resulting in death are reported to EC and RA within 7 days [ClinO Art. 41].
- All other SUSARs are reported to the EC and RA within 15 days [ClinO Art. 41].

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) including RA specifications.

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

- Based on protocol, all AE information should be collected by the investigator and reported to the sponsor in a standardised manner, (CRF documentation; AE reporting form).

– For category A clinical trials, AE documentation is not required (but general PV rules have to be followed. For further reference, please also check www.swissmedic.ch.
– For category B clinical trials, AE documentation in a standardised manner is mandatory if stated in the protocol or if requested by the EC/ CA [ClinO Art. 39].
– SAEs, not exempted by the protocol, should be reported to the sponsor in a standardised manner regardless of causality.

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

13.6.3 Annual Safety Reports for Investigational Medicinal Products

Annually and throughout the duration of the trial, the investigator compiles all safety issues in an annual safety report to be submitted to the EC. For category B and C trials, the sponsor submits the annual safety report to the national RA and EC [ClinO Art. 43]. If applicable, the international DSUR format is also acceptable according to ICH-E2F.

– The annual safety report provides current safety knowledge by identifying and describing potential risks regarding active **substances/medicinal products** during clinical trials.
– The safety report should contain a precise, critical summary of the medicinal product's safety profile including relevant safety aspects and any detrimental effects. A list in table form showing **Serious Adverse Events (SAE)** should also be appended, including detailed presentations of SUSARs 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 trial in Switzerland (number of sites open/closed, number of participants recruited/ recruitment closed, and number of SAEs/SUSARs).
– For EC submission, the implemented administrative amendments are added to the report including a current site staff list.
– In any case, the sponsor should keep a list of all AEs reported by investigators. This list should be provided to the RA (e.g. Swissmedic) upon request.

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

13.6.4 Safety Reporting for Medical Devices

For clinical trials with medical devices, severe incidents and health hazards, as well as corrective measures should be reported to the RA and EC [ClinO Art. 37, 38 and 42].

– Corrective measures considered important for the protection and health of participants should immediately be implemented by the sponsor and investigator. The EC and RA should be informed within 2 days.
– All severe device or possibly device-related incidents having occurred in Switzerland should be reported within 7 days to the EC and RA.
– The initial report should be submitted within the above timeframes, a more detailed report should follow later.
– EC and RA should be notified immediately regarding severe incidents having occurred abroad.
– EC and RA should be notified immediately of events or issues such as investigator non-compliance, leading to safety re-evaluation of the rights of clinical trial participants in Switzerland being compromised.
– For category A medical device trials the sponsor will follow safety reporting as stated in the Ordinance on Medical Devices[25] Art. 15 (1).

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

13.6.5 Annual Safety Reports for Medical Devices

For category C medical device trials, an annual safety report should be sent to both the EC and the RA for the entire duration of the clinical trial [ClinO Art. 43]. This 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 clinical trials performed with the investigational device
– An analysis of the clinical relevance and acceptability of the events, including an evaluation by the sponsor regarding the safety for participants
– Any risk-reducing measures taken or planned

For details refer to the websites of Swissmedic and swissethics.

25 Medizinprodukteverordnung (MepV) / Ordonnance sur les dispositifs médicaux (ODim)

13.6.6 Safety Reporting for Clinical Trials of Transplantation and other Clinical Trials

For clinical trials of transplantation of human organs, tissues and cells, guidelines as described in Chapter 13.6.2 apply. Responsible RA is the Federal Office of Public Health [ClinO Art. 57]. For details refer to www.transplantationsdaten.admin.ch.

For other clinical trials, the mentioned guidelines as described in Chapter 13.6.2 apply. Serious adverse events related to the intervention must be reported to the EC within 15 days [ClinO Art. 63].

13.7 Change Control Process

As applicable, the CTU shall emphasise that any changes implemented during the course of a clinical research are documented and reported to the RA and EC.

13.7.1 Amendments

Prior to being implemented, the investigator/sponsor is responsible to inform the EC (and RA if applicable) regarding any significant deviation from or changes to the running of the clinical research.

Exceptions to the rule are safety amendments, which can be implemented immediately due to immediate hazards to participants.

Non-significant deviations from or changes to the clinical research must be included in the annual safety report to be submitted to the EC as applicable. In contrast, relevant changes should be forwarded as soon as possible [ClinO Art. 29, 34 and 55[26]]. In contrast, the RA requests these documents upon occurrence.

- Any planned changes to protocol procedures should be formalised in a **protocol amendment**.
- Implications with respect to safety risks to trial participants, data quality aspects, including trial relevant processes should be assessed. Measures to mitigate these risks should be implemented and documented.
- The amendment should be forwarded to participating investigators for submission to EC. If applicable, the sponsor submits the amendment for approval to RA.
- The amendment should be forwarded to participating the EC and to the RA, if applicable.
- Only after approval by EC and RA can the amendment be implemented.
- In the event that the CRF is affected by the amendment, applicable changes or adaptations should be made. This would also entail to changes to the patient information and consent. (See below Chapter 13.7.4 Informed Consent Form).

13.7.2 Protocol Deviations

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

- Documents concerning protocol deviations should be filed in the ISF.
- In the event of significant non-compliance, the sponsor is responsible to conduct a root cause analysis and implement corrective and preventive measures.
- The sponsor and, if applicable, the EC and the RA should be informed.

13.7.3 Advertisements

Any newly available important information regarding the product under investigation and/or protocol amendments may trigger a revision of participant advertisements needed for recruitment.

- Any advertisement updates (e.g. newspaper ads, posters) require re-approval by the EC
- For social media advertisements refer to the swissethics website.

13.7.4 Informed Consent Form

The newly available important information regarding the product under investigation and/or protocol amendments may trigger a revision of the participant information sheet and/or ICF. If it is anticipated that changes might affect participant willingness to participate in the clinical research, he/she should be provided with the new information and be given the opportunity to re-consent [ICH GCP 4.8.2].

- The consent form and participant information sheets should be updated (strictly respecting version control) and submitted to the EC for approval. Only upon approval can the newly updated versions be presented to the participants.
- All currently enrolled participants should be provided with the new updated information.
- Procedures for obtaining written informed consent should be repeated as described (see Chapter 13.3 Informed Consent Process).

13.7.5 Case Report Form Management

Any change or correction to the CRF should be version-controlled and, if applicable, submitted for approval to EC.

26 Also refer to ICH GCP 4.5.2

For details refer to Appendix 2: Data Management Guidelines.

13.7.6 Interim Analyses

Interim analyses should be performed as stated in the protocol, respectively in the SAP or earlier, if required by an independent data management board or data management committee. For delivery and **coding** of data for interim analyses refer to Appendix 2: Data Management Guidelines).

13.7.7 Closure of Single Sites

In the event that one or multiple sites of a multisite clinical research close(s) or decide to close the site, it is the responsibility of the investigator to inform the EC [ClinO Art. 38].

13.8 Clinical Research End

The administrative and regulatory closure of a trial site is initiated after the last participant has had his/her last visit (Last Patient Last Visit) followed by data base lock.

- As defined in ICH GCP 8.4, all essential documents should be filed in the ISF and/or TMF.
- **Source Data Verification** should be completed, all queries should be resolved, a medical review should be performed, and the data should be archived.
- The database should be locked prior to final analysis. For details refer to Appendix 2: Data Management Guidelines.
- The monitor should perform a site closeout visit.
- Registries where the clinical research is registered should be updated.

14. Completion Phase

The completion phase begins once the last participant has had his/her last visit and ends when all clinical research documents have been archived.

With the completion phase the clinical research project is brought to an end. It includes aspects such as data analysis, publication of results, archiving, and reporting to the EC and the RA.

14.1 Reporting to the Ethics Committees and Competent Authorities

The EC and RA should be notified regarding the completion or any premature termination of the clinical research [TPA Art. 54.7a and ClinO Art. 38]. EC notification is managed through the BASEC portal. In the event of a multisite study, the sponsor or **coordinating investigator** (if not otherwise delegated to a third party) makes the applicable BASEC submission by selecting additional local ECs to be informed.

The sponsor should inform EC and RA of the end of the clinical research after the last visit of the last participant at the last Swiss site. Swissmedic also expects to be informed of the premature termination of a clinical research at an individual site, e.g. because of a lack of participants or for safety reasons.

The sponsor should

- Inform EC and RA of the clinical research completion within 90 days.
- In the event of premature termination, notification should be performed within 15 days, including any consequences thereof.
- Submit a final CSR to the RA within 12 months upon completion or premature termination of the clinical research. In research projects involving radiation sources, the project leader submits a final report to the FOPH [HRO Art. 23].

14.2 Data Analyses (and Statistics)

If delegated to the CTU, the clinical research analyses shall be carried out in accordance with a SAP on behalf of the customer.

- Analysis is performed once the database has been locked.
- A competent person using a validated software system and/or programme should perform the analysis.
- Analytical 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.
- A statistical analysis report should be created with detailed results of the analysis. This report should be forwarded to the investigator and sponsor for interpretation and publication of results.

For additional information, refer to Appendix 2: Data Management Guidelines.

14.3 Clinical Study Report

In accordance with ICH GCP 5.22, every clinical trial shall be reported to the RA and EC latest one year after trial completion, discontinuation or interruption [ClinO Art. 38]. The final **Clinical Study Report (CSR)** should report the results of the clinical trial in a clear, complete and objective way. The CTU may provide support in compiling the report as specified in the contract/SLA. When writing the CSR:

- The ICH E3 Guideline should be followed, which gives detailed guidance on the structure and content of CSRs in order to be complete, free from ambiguity, and being well organised and easy to review.
- The ICH E3 Guideline is mandatory for pivotal research and suitable for the reporting of an individual clinical trial of any therapeutic, prophylactic or diagnostic agent conducted in clinical trial participants.
- In certain cases, abbreviated reports may be acceptable, e.g. for uncontrolled clinical trials or other clinical trials not designed to establish efficacy.

Once validated by the sponsor, the report should be distributed to investigators, relevant RA, and EC at their request.

14.4 Information of Participants

According to the Declaration of Helsinki (DoH), participants are entitled to be informed about the overall results of the clinical research upon request. The CTU may provide support for the preparation of participant related communication material.

- In blinded projects, participants should be informed of the intervention they received after the un-blinding.
- Communication material to participants should be tailored so as to be readily understood. Thus, it should be written in an uncomplicated language, if possible avoiding medical terminology, ideally provided in the participant's first language.
- The communication material should be provided to the investigator(s) for distribution to participants interested in the project.

14.5 Archiving

Data and document archiving processes for sponsor, site investigator(s), and CTU should be complemented as required by legal and regulatory requirements [ICH GCP 4.9.5, 5.5.6, 5.5.7], including provisions set forth in the contract/SLA.

14.5.1 Archiving of Data and Clinical Research Documents

- The management of paper and electronic filing should be defined in a documented procedure.
- It should be ensured that archived documents remain complete, legible and accessible throughout the required archiving period.
- Location of project record should be documented to ensure ongoing access.
- Access should be restricted and limited to duly authorised personnel.
- For IMP clinical research, trial data should be archived for at least 10 years after clinical research completion/premature termination for IMP clinical research, 15 years for implantable medical devices and 20 years for standardised transplants and blood products [ClinO Art. 45]. For international trials other timelines may apply.
- Upon completion of the archiving period, all records pertaining to the clinical research can be destroyed. Destruction should be coordinated, monitored and documented.

For details on electronic data storage refer to Appendix 2: Data Management Guidelines.

14.6 Publication

As required by the Declaration of Helsinki, clinical research data shall be reported free of ambiguity and in a complete, adequate, accurate and transparent manner. The CTU can provide assistance and shall ensure that international reporting standards are followed.

14.6.1 Publication Policy

The CTU should ensure that publication policies as defined in the protocol or in an agreement are followed.

- Sponsors have the ethical obligation to publish their research results, regardless of the outcome (positive, negative or inconclusive results).
- Sponsors are accountable for the completeness and accuracy of their reports.
- Sources of funding, institutional affiliations and conflicts of interest should be clearly stated.

14.6.2 Publication Standards

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

- Type of research determines the established reporting standards that should be followed, such as CONSORT[27] for randomised controlled clinical research or STROBE[28] for observational trials.
- Articles and presentations should be complete, balanced and clear.
- Reference to the unique clinical research identification number should be included in all articles and presentations.
- Interpretation of results should be unbiased, scientific and relevant.
- Discussion of results should be unbiased an in context with other relevant research, and the evidence cited should be balanced.
- Limitations with respect to design and methodology should be described.
- Related findings from other researchers should be cited, especially if previous results conflict with the reported results.

27 CONSORT – Consolidated Standards of Reporting Trials

28 STROBE – STrengthening the Reporting of OBservational studies in Epidemiology

14.6.3 Authorship/Contributorship

The uniform requirements for manuscripts submitted to biomedical journals published by the ICMJE[29] should be respected.

- Authorship credit should be based on substantial contributions to:
  1. The conception or design; or acquisition, analysis, or interpretation of data; and
  2. Drafting of article or contribution of important intellectual content; and
  3. Final approval of the version to be published; and
  4. Agreement to be accountable for all aspects of the clinical research in ensuring the questions related to the accuracy or integrity of any part of the clinical research are appropriately investigated and resolved.
- Contributors who do not meet all requirements do not qualify for authorship. They should be listed in the acknowledgment section.
- The CTU should ensure that its contribution to the clinical research is acknowledged in the publication.

14.6.4 Disclosure of Conflicts of Interest

During the publication process, all participants should disclose any relationship that might be viewed as a potential conflict of interest, e.g. financial or personal relationships that might duly influence (bias) their approach and actions towards the publication.

29 ICMJE – International Committee of Medical Journal Editors http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

15. CTU PROJECT CLOSURE

15.1 Project Management

The CTU shall perform the administrative closure of the project including an overall project assessment in order to identify potential improvement aspects benefiting future research.

15.1.1 Debriefing

- Upon project termination, a debriefing meeting should be organised involving all relevant external project partners. Discussion points may address e.g. positive and negative collaboration aspects, potential lessons learned, project impact assessment.

15.1.2 Project Evaluation

The project leader should perform an overall project assessment. He should identify and evaluate future optimisation potential. Aspects to address are:

- A review of the budgetary, logistic and administrative aspects
- An evaluation of customer and partner satisfaction (questionnaires, complaints)
- Corrective actions based on internal and external audit findings
- A final review of the key performance indicators, the non-conformities and implemented corrective actions
- Planned assessments regarding the effectiveness of implemented corrective actions

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Supporting Documents

Quality Policy of the CTU network (current version).

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