Module 4 GCP-R2 (2016)

INTRODUCTION TO CLINICAL RESEARCH

PART 1. OBJECTIVES OF GOOD CLINICAL PRACTICE IN CLINICAL RESEARCH

Worldwide acceptance of clinical data requires harmonization in the conduct of clinical trials. Clinical trials help to better understand diseases and their treatments and ensure an adequate evaluation of the safety and efficacy of new medicinal products or new indications of a marketed product before marketing authorization is granted.

Clinical research in general and drug development in particular are complex, scientific, regulatory-driven and long-term activities. In a clinical trial, the therapeutic intervention of interest may be a medicinal product, but can also be a medical device, or the combination of both, or any other clinical investigations that may have an impact on the safety and well-being of human subjects.

Drug development includes pharmaceutical development; new medicinal product formulation, preclinical activities (in laboratories and on animals) and clinical development (on humans) and requires several steps before marketing authorization is granted.

In this **Good Clinical Practice** (GCP) training module, we focus on clinical research where administration of a medicinal product is the therapeutic intervention. The investigation may concern a newly discovered compound, often called new medicinal entity, or a recognized medicinal product for which a new indication or a new formulation is being developed. In all circumstances the therapeutic intervention is the administration of a so-called **Investigational Medicinal Product** (IMP).

Good Clinical Practice principles are recommended for all interventional clinical trials, including those with medical devices or other therapeutic interventions. Due to variations in rules and laws, this training module only focuses on “interventional clinical research of IMP”.

PART 2. PRECLINICAL ACTIVITIES

This section deals with pre-clinical activities to provide the course participants with an insight into the work that is required before the first administration of a new medicinal product in humans can take place. A full review of pre-clinical research requisite falls outside the scope of a basic GCP training program. Course participants who are interested in this particular topic are advised to look at the **Investigator Brochure** (IB) and/or consult qualified pre-clinical experts. The minimum information that should be included in an IB is delineated in ICH-GCP guidelines section 7.

2.1 Introduction

Preclinical development included drug discovery and various preclinical research activities before a clinical trial can start in human. Drug discovery activities aim at identifying molecule with therapeutics properties and the process involves the identification of molecule, synthesis, characterization, screening, and assays for therapeutic efficacy. Once the value of a compound has been identified, studies in animals will provide descriptive information on the efficacy, toxicity, pharmacology, derivative and formulation of a compound.

The primary goals of preclinical safety evaluation are:

1. to identify an initial safe dose and subsequent dose escalation schemes in humans;
2. to identify potential target organs for toxicity and for the study of whether such toxicity is reversible; and
3. to identify initial safety parameters for clinical monitoring in humans which include acute, sub-acute and chronic toxicity, carcinogenicity, reproductive toxicity (fertility, teratogenicity, peri- and postnatal development), genotoxicity and toxicokinetics.

Different types of products may undergo different preclinical tests. The minimum number and types of tests to be done in pre-clinical settings are defined by regulatory bodies. The most common assessments are safety pharmacology studies, pharmacodynamics, and pharmacokinetics (absorption, distribution, metabolism and excretion (ADME)) studies. These tests provide an estimation of the initial safety of the compound and the starting dose that will be used in the “first in human” clinical trials, also called phase I trials.

Assessments of pharmaceutical preclinical studies should be done as described in ICH “Safety Guidelines” (“S”).

2.2 Preclinical toxicity studies

This paragraph provides an example of relevant preclinical study results that must be available before clinical trials in humans can be conducted. A brief overview of the minimum toxicology studies required by the principal regulatory agencies is presented. Investigators should expect to find all IMP preclinical study results in the IB.

There are currently regional differences for the minimum duration of repeated dose toxicity studies; 2 weeks in the EU and the USA, and 2 weeks non-rodent and 4 weeks rodent in Japan.

Repeated dose toxicity studies must be performed in two species (one being non-rodent) for a duration of 2-4 weeks to support human **pharmacology trials (phase I)** and up to two weeks to support **therapeutic exploratory trials (phase II)**. In addition, 1-, 3-, or 6-month toxicity studies would support clinical trials in humans for up to 1-, 3-, or 6-months IMP administration, respectively. Six-month rodent and chronic toxicity studies (chronic toxicity studies assess the long-term toxic as well as carcinogenic potential of various substances) in non-rodent would support clinical trials of longer duration than 6 months. For **therapeutic confirmatory trials (phase III)**, the recommendations for USA and Japan follow the phase I and II approaches. The minimum requirements are for the EU a one-month study in two species (one non-rodent) to support clinical trials of up to two weeks duration. Three-month toxicity studies must be available for clinical trials of up to one month duration and six-month toxicity studies in rodents and three-month studies in non-rodents to support clinical trials of up to three-month duration. For long-term clinical trials, a six-month study in rodents and a chronic toxicity study in non-rodents must be performed.

The information collected during preclinical studies should be part of the safety assessment to support the conduct of clinical trials in humans and the approval of a marketing authorization

Before initiating clinical trials in humans, the sponsor must compile extensive information on:

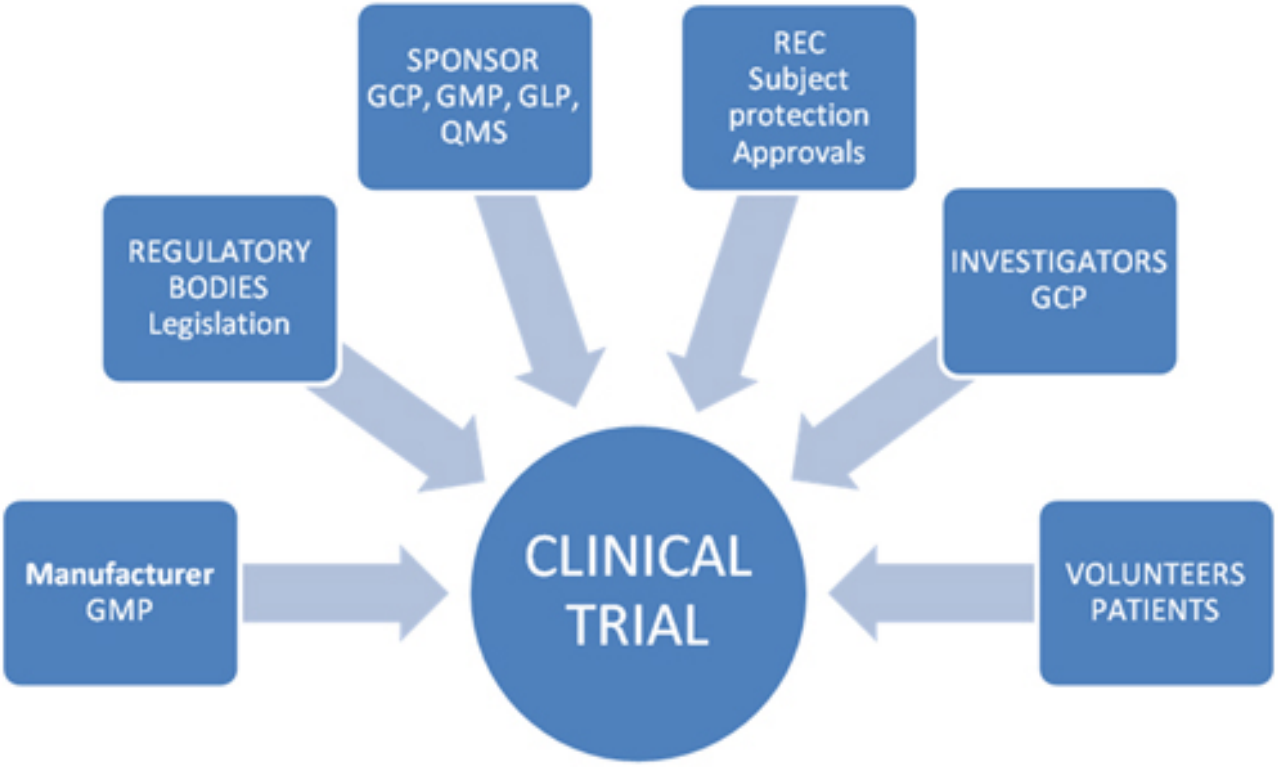
- preclinical experiences in vitro and in-vivo laboratory animal testing on the compound. Preclinical assessments include short-term and chronic toxicity evaluation.
- clinical experiences (if any)
- review of the literature

The IB must contain all information on the product manufacturing, preclinical data and clinical experiences. The IB must be updated at least once a year or more frequently if new information becomes available.

- ICH-Preclinical Testing of Biotechnology-Derived Pharmaceuticals S6 (R1), 2011
- ICH-General Considerations for Clinical Trials E8, 1997
- ICH-Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies S3A, 1994
- ICH-S2(R1)Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, S2 (R1), 2011
- ICH-Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals S1A, 1995
- ICH-Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5 (R2), 2000

- ICH-Duration of Chronic Toxicity Testing in Animals (Rodent and Non-rodent Toxicity Testing) S4, 1998
- EU CPMP/ICH/302/95 note for guidance on safety studies for biotechnological products
- EU CPMP/ICH/286/95 (ICH M3) non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
- EU CPMP/ICH/302/95 (ICH S6) preclinical safety evaluation of biotechnology-derived pharmaceuticals
- EU CPMP/ICH/539/00 (ICH S7A) safety pharmacology studies for human pharmaceuticals
- EU CMPM/ICH/384/95 (ICH S3A) toxicokinetics: the assessment of systemic exposure in toxicity studies
- US FDA, "Single Dose Acute Toxicity Testing for Pharmaceuticals; Revised Guidance" 61 FR 43934, 43935, August 26, 1996.

PART 3. CLINICAL TRIALS



3.1 Definitions

Clinical trial: As per ICH-GCP, a clinical trial is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational products and/or to identify any adverse reactions to an investigational product and/or to study absorption, distribution, metabolism, and excretion of an investigation product with the object of ascertaining its safety and/or efficacy. This terms clinical trial and clinical study are synonymous.

Interventional clinical trial: In an interventional trial, the investigators give the trial participant a particular medicinal product or other intervention. Usually, the trial compares the treated participants to participants who receive no treatment or standard treatment.

Treatment trial: A treatment trial is designed to evaluate one or more experimental treatments, new combinations of medicinal products, or new approaches to non-drug therapies (surgery, radiotherapy)

Prevention study: A prevention study is carried out to identify better ways to prevent diseases in a population who have never had the disease or to prevent a disease from recurring. Prevention studies may include medicinal products, vitamins, or vaccines.

Quality of life studies look at ways to improve the quality of life for patients with chronic diseases.

Non-interventional trial: As per EU Directive 2001/20/EC, this is a trial where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

Others: There are other clinical trial definitions, such as “diagnostic trials” conducted to find better diagnostic tests, “screening trials” to detect certain diseases or health conditions, or “compassionate use trials” or “expanded access studies” to provide unapproved medicinal products to patients for whom no other alternative effective treatments are available.

3.2 GCP in non-interventional clinical studies

As per EU laws and regulations, full implementation of GCP is not required in non-interventional clinical studies. The topic will not be covered in the framework of this course.

But it must be noted that any research involving human subjects, whether in an interventional or a non-interventional approach, should be conducted in accordance with ethical principles, respect to persons, beneficence and justice (CIOMS). The CIOMS guidelines on epidemiological studies were published to draw the attention of investigators, sponsors and REC to the need to consider the ethical implications of any research on human subjects as even non-interventional studies can induce physical harm. Non-interventional studies should also be carefully planned, involving all parties, ensuring the protection of confidential data and study participant well-being and follow GCP whenever possible and ethically justified.

3.3 Clinical Trial Principles

Clinical trials evaluating pharmaceuticals and biopharmaceuticals in healthy volunteers and in patients must be scientifically sound and ethically justified. Clinical trials may be designed to evaluate the safety and efficacy of new compounds, new indications or to evaluate whether a compound is better than a standard treatment, or is as good as the treatment available on the market, or has a pharmaco-economic advantage. Those trials are defined as “interventional” clinical trials and their conduct is highly regulated.

3.4 Clinical Trial Phases

Clinical trials involving new pharmaceuticals or biopharmaceuticals are commonly classified into four phases, and the development of the product will in general proceed through all four phases over a period of 5-12 years.

Some sponsors or research organizations may use other terms such as phase Ia, phase Ib, phase I-II, phase IIb, or phase IIIb. As these terms do not have a “standard” definition, they will not be covered in the framework of this course (see comments in the forewords this module).

- **Phase I:** Phase I clinical trials are the first-stage of testing in humans. Normally few (<20-80) healthy volunteers participate. In some disease areas (e.g. oncology), phase I trials are performed in patients as the IMPs are given at toxic doses. Phase I trials are designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the product. Phase I trials include dose escalation or dose-ranging trials and the starting dose to be used in human is derived from the animal studies. As little is known about the product used in a phase I trial, it is important that the clinical trial protocol defines prospectively the stopping rules, especially in case of unacceptable toxicity. The REC should pay special attention to this point when evaluating the protocol.
- **Phase II:** Phase II trials are performed in a larger patient population (100-300). The design is disease-oriented and assesses the clinical efficacy of the product and short-term safety profile in the selected population. Phase II trials may be defined as “phase II pilot trials” design to assess preliminary efficacy or dose-response or dose regimen, for instance.
- **Phase III:** Phase III trials are large scale trials (can involve several hundred/thousands patients) comparing the new treatment with the current available alternatives or a placebo or no treatment. Placebo may be requested by health authorities although active treatments might be available on the market. The primary aim of the trial is to demonstrate the efficacy and safety of the new product or new indication in a large population. Phase III trials are often referred to as “pivotal” trials as they are supporting the indication in the registration dossier.
- **Phase IV:** Phase IV studies are studies initiated after marketing authorization has been granted. The study is designed to detect any rare or long-term adverse reactions or drug-drug interaction in a population at large or in a specific population group. Phase IV studies can also include “pharmaco-economic studies”, “efficacy efficiency or effectiveness evaluation in routine medical practice”, etc.

It must be noted that trials performed for drug reformulation, new formulation, label extension, new schedule of administration, or new indications are clinical trial activities falling under pre-registration activities and are classified as interventional trials.

With new drug development approaches, new terminologies appear. The following terms lack rigorous definitions and exact usage varies between authors, scientists, methodologists, biostatisticians and institutions. The descriptions given below are intended to be informative and practically useful:

- **Proof of mechanism:** ***proof of mechanism*** trials usually relate to the earliest stages of drug development, often pre-clinical (for instance before the drug is given to humans, or before given to research animals). It could be based on showing that the drug interacts with the intended molecular receptor or enzyme, and/or affects cell biochemistry in the desired manner and direction.
- **Proof of concept:** ***proof of concept*** trials are designed to collect specific efficacy information in humans at an early stage of drug development such as when biomarkers are used as surrogate endpoint used to guide whether or not further testing is needed. Surrogate

endpoints are mainly based on laboratory blood tests or imaging investigations like X-ray or CT scan. The basic principle is to increase efficiency by allowing early go/no go decisions. In other terms, proof of concept trials help to eliminate too toxic or inefficient compounds early in the development process or provide early evidence of potential clinical efficacy.
- **Proof of principle:** ***proof of principle*** trials often relate to later clinical development, typically involving larger numbers of patients treated at doses and durations representative of marketed use, and in randomized comparison to placebo and/or existing active medicinal products. They aim to show convincing, statistically significant evidence of efficacy and to give a better assessment of safety than is possible in smaller, short term studies. A decision is made at this point as to whether the drug is effective and safe, and if so an application is made to regulatory authorities for the drug to receive permission to be marketed for use outside of clinical trials.

- ICH-General Considerations for Clinical Trials E8, 1997
- EU EMEA/CHPM/SWP/28367/07, guideline on strategies to identify and mitigate risks for first-inhuman clinical trials with investigational medicinal products
- US 21 CFR Part 312 - Investigational new drug application ⇒ Sect. 312.21
- CIOMS International Ethical Guidelines for Epidemiological Studies. Council for International Organization of Medical Sciences (CIOMS) and World Health Organization (WHO) Feb 2008.

Before embarking on clinical trials, the following questions should be raised:

- why do I need a clinical trial?
- what are my objectives?
- which hypothesis will be valuable?
- how can I best use my biostatistician to optimize the trial design
- what I am going to do with the results, knowing that clinical results whether positive or negative should be publicly available.

To help answer these questions, it is necessary to have detailed knowledge of the disease and of the pharmacology, biochemistry and toxicology of the drug used in the clinical trial. This also requires knowledge of what has already been published.

PART 4. AVOID BIAS

4.1 Principles

If clinical trial conclusions provide inaccurate; unrealistic results (e.g. exaggerate benefit of a new treatment), then the trial does not give new information on the treatment of the disease under consideration. Such results may be qualified “unethical”. Therefore, proper clinical trial design should avoid bias and incorrect conclusions.

Scientific clinical trials should take into account trial design (including possible bias), the number of participants (too few participants cannot reach a reliable conclusion), and the publication strategy (none published findings allow other to perform the same clinical trials that may have negative results). It is important that clinical trial results are published as soon as possible after the completion of the trial.

Biased results can be avoided by choosing objective rather than subjective parameters, blinding the treatment allocation and randomizing participants with or without stratification process. In other terms, to ensure the validity of the data, there are basically three possible sources of errors that must be taken into account:

- **chance** (or error in precision) is caused by “random variation” which determines whether the results are due to “chance”. This “random variation” is controlled by the sample size (adequate sample size calculation).
- **bias** is caused by “systematic variation” (e.g. patient’s selection, outcome measurements), or error in the measurement of a variable. There can be three types of bias:
    - **selection** of participants or their treatment allocation which can be controlled by a random selection and random allocation to treatment group (randomization design)
    - **measurement** of outcomes may be due to instruments, or different interpretations of the data by different investigators or health professionals. This can be controlled by blinding the treatment allocation and the review by an independent data review monitoring board.
    - **analysis** bias can be reduced by including all trial participants and by performing both an intent-to-treat and a per protocol analysis.
- **confounding factor** is a factor that has a prognostic linked to the outcome of interest and can generate error in the interpretation. This can be minimizing by stratifying the population or using other statistical techniques to adjust for confounding.

Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimizing any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems and also to handle the problems that can occur in the analysis of data.

4.2 Blinding

Blinding is intended to limit the occurrence of measurement bias (conscious and unconscious) in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of participants, their subsequent care, the attitudes of participants to the treatments, the assessment of end-points, the handling of withdrawals, or the exclusion of data from analysis. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

As far as possible, clinical trials should remain under blind conditions. Breaking of the blind is a serious matter, but may be needed for safety concerns. Breaking of the blind (for a single participant) should be considered when knowledge of the treatment assignment is deemed essential by the investigator for the best interest of the participant's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence.

The sponsor must have specific procedures for breaking the blind in the safety reporting process, such as reporting unexpected serious adverse drug reactions and other expedited reports to health authorities. The procedure and timing for revealing the treatment assignments should be documented.

In multicenter clinical trials, you may have a "blinded" efficacy endpoint committee but an unblinded "safety review committee".

4.3 Randomization

Randomized controlled trials are often assumed to produce unbiased evidence. A randomized clinical trial is the process of observing the outcome of a random allocation of the intervention of interest. The randomization schedule of a clinical trial documents the random allocation of treatments to participants. In the simplest situation it is a sequential list of treatments (or treatment sequences in a crossover trial design) or corresponding codes by participant number.

In multicenter trials, the randomization procedures should be organized centrally. It is advisable to have a separate random scheme for each center, such as to stratify by center or to allocate several blocks to each center.

The exact randomization procedure must be described in the protocol.

4.4 Stratification

Stratifying the population means dividing the population units into homogeneous groups (STRATA) and drawing a simple random sample from each group. More generally, stratification by important prognostic factors measured at baseline (e.g. severity of disease, age, sex, etc.) may sometimes be valuable in order to promote balanced allocation within strata; this has greater potential benefit in small trials when equal treatment allocation across significant prognostic factors is critical in particular in multicenter clinical trials. The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance and is logistically difficult. Factors on which randomization has been stratified should be accounted for in the analysis of the results.

Stratifying by center is a common procedure applied in multicenter clinical trials.

4.5 Sample Size

The **sample size** estimation should be sufficient to achieve the predetermined power of the clinical trial results and to ensure that the primary objective of the trial can be answered.

Larger sample sizes generally lead to amplify precision when estimating unknown parameters. A predetermined Type I error (α) should be taken into account in the sample size calculation.

The larger the variability in the outcome measure, or the smaller the difference in treatment effect to be demonstrated, the larger the number of trial participants is required. The protocol needs to include a justification of its sample size calculation. Sample size calculations should refer to the number of trial participants required for the analyses of the primary objective.

A clinical trial with a too small number of participants brings a considerable risk of failing to demonstrate a treatment difference when one, in fact, really exists. Such clinical trials have a large type II error, meaning that it can produce false negative results.

4.6 Type I & II Errors

4.6.1 Type I error

- **α** generally called the Type I error is the probability of detecting a significant difference when the treatments are really equally effective (risk of false positive results or 1- specificity). α is often set at α=0.05

4.6.2 Type II error

- **β** generally called Type II error is the probability of not detecting a significant difference when there really is a difference (risk of false negative results or 1- sensitivity)

4.7 Power

The **power** of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is false (i.e. the probability of not committing a Type II error or making a false negative decision). The power is in general a function of the possible distributions, often determined by a parameter, under the alternative hypothesis. As the power increases; the chances of a Type II error occurring, decrease. The probability of a Type II error occurring is referred to as the false negative rate (β).

The power is equal to 1 − β, known as the sensitivity. Although there are no formal standards for power, most clinical trial designs have a power of at least 80%, 90% or 95%. For a given power, the larger a clinical trial, the smaller the difference it is capable of detecting. As the power increases the chance of a Type II error occurring decreases. As for the significant level, the power is decided before the data is collected (defined in the protocol and the statistical analysis plan) and is vital in the sample size calculation.

4.8 P value

Statistical tests are used to calculate the probability (P) that a difference as large as or larger than that seen in the trial data would occur by chance if the treatments were actually identical in efficacy.

- ICH-Statistical Principles for Clinical Trials E9, 1998

PART 5. BASIC CLINICAL TRIAL METHODOLOGY: TRIAL DESIGNS

Clinical trial design is driven by the objective of the study, type of intervention, study population characteristics, and when applicable, the availability of treatment alternatives. In this GCP course we focus on interventional clinical trials, in particular trials assessing medicinal compounds in human subjects.

When the objective of the study is to learn more about the behavior of an investigational medicinal product (IMP) in the human body there is a well-developed series of study designs, applied usually with healthy human volunteers, to study absorption, distribution, metabolism and excretion (**ADME or pharmacokinetic studies**) of the IMP, administered in one or more delivery forms. Sometimes modified ADME study designs enroll patients to study pharmacokinetics in special populations (such as in kidney function impairment), or because of the toxic nature of the IMP at therapeutic dosages (such as in cancer).

When the objective of the trial is to investigate the effect of a therapeutic intervention, the trial population may consist of patients with a particular condition, defined by in- and exclusion criteria of the protocol. A **placebo-control** group or placebo treatment period may be chosen in studies where providing no treatment is an acceptable choice for the condition under study, no effective treatment is available, or participation in the study does not disadvantage the participants by withholding available treatment options. The latter is called clinical equipoise, which means the community of experts genuinely believes no evidence-based medicinal product is preferred over placebo in the population with the condition under study. See TRREE modules 2.1 and 3.1.

In case a placebo treatment is considered ethically not acceptable, a comparator group or comparator treatment period may be included in the design.

If technically possible, by means of an indistinguishably identical method of administration of placebo or comparator and active IMP, a **blinded trial** design is preferred to avoid bias. Most often, the participants as well as the investigator and other staff, including those of the sponsor, are blinded to the treatment until the data are analyzed; this is called a **double-blind** study Should only the participants be blinded to the treatment modality it is called a **single-blind** study.

The **data analysis of a blinded trial** is not conducted before all results of all participants have been collected and fully assessed in a blinded approach. In exceptional circumstances, taking into account special statistical and organizational conditions to warrant data integrity, one or more interim-analyses may be scheduled to detect an early and meaningful treatment effect. Should a pre-defined threshold of efficacy (or safety concern) be detected in the interim analysis, the trial will then be discontinued and analyzed fully with the limited data set. An interim analysis may be scheduled, for example, to ensure an IMP is made available as soon as possible and effective treatment is not unduly withheld to patients by the additional time it takes to complete the full clinical trial. An interim analysis is conducted to avoid unnecessary exposure of more trial participants, if a treatment is particularly beneficial or harmful compared to the concurrent placebo group while the trial is on-going.

In **randomized trials**, the allocation of treatment modality (active IMP, placebo or active comparator) is by chance. See section 4.3, on randomization. The subjects enrolled in this way can be:

- each randomized and treated consistently with either placebo (or active comparator) or active IMP until the end of study: **parallel group** design;
- each treated in sequence or random order with placebo (or active comparator) and the active

IMP: **cross-over** design;
- administered IMP in trials with a **factorial design**, whereby elaborate schedules of sequential treatment with active IMP alone and in combination with other active study drugs and/or placebo are possible. For example, when the combined effect of two actives versus the effect of each of the agents separate is investigated.

When certain known pre-existing conditions potentially affect the study results (confounding, see above, section 4.1), the randomized treatment allocation may be modified. For example, in a multicenter trial, each of the trial units may have an equal allocation of trial participants in the treatment groups. Such **stratification** intends to control confounding and make the study more efficient by reducing the overall number of trial participants needed.

When blinding is not possible or not needed because of the trial objective, this type of trial is called **open-label**. Open-label design may or may not have a comparator group. In case a comparator group (active product or no treatment) is included in the design, the randomization procedure and the treatment allocation are similar to that of blinded trials. Open-label design always evaluates an active IMP to against either no treatment or another active comparator; open-label design never includes a placebo comparator group. In open-label trial design, the investigator and the participants are aware of the treatment allocation.

Generally, trial designs are modeled to demonstrate a treatment difference of a given magnitude between treatment groups: **superiority trial**. Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo more than once in double-blind, randomized placebo-controlled trials, or superiority to an active control treatment in trials with a double-blind, randomized comparator-control design. Other study designs are scientifically less persuasive, but for each trial the appropriateness of randomization, the ethically acceptable use of placebo and/or the choice of comparator need to be considered in clinical context.

Under certain circumstances, trials with the IMP and one or more comparators, in blinded or open-label design may be used to demonstrate that the IMP is not clinically inferior to a comparator treatment: **Non-inferiority** clinical trials. Similar statistical considerations regarding the probability to demonstrate a minimally detectable difference apply to determine the sample size of non-inferiority trials. In the protocol, the lower margin acceptable must be specified and clinically justified.

Equivalence trials are designed to demonstrate that one treatment is as effective as another. A special case is bioequivalence trials, for example, to demonstrate bioequivalence of a generic product with the registered and already marketed (innovator) product. A bioequivalence study intended to demonstrate that, within a pre-defined statistical probability, absorption, distribution and excretion parameters of the generic are equivalent to those of the innovator. In some situations, efficacy equivalence trials are undertaken for other regulatory reasons such as demonstrating the clinical equivalence of a generic product to the marketed product; for example, when the compound is not absorbed and therefore not present in the blood stream. Both the upper and lower margins (of the relevant pharmacokinetic or efficacy parameter) should be specified in the protocol and clinically justified.

- ICH-Statistical Principles for Clinical Trials E9, 1998

INTRODUCTION TO GOOD CLINICAL PRACTICE

PART 6. HISTORICAL BACKGROUND

WHY SO MANY GOOD PRACTICE GUIDELINES, LAWS AND REGULATIONS?

Many guidelines, laws and regulations governing clinical research in general, and clinical trials in particular, resulted from some past experiences associated with serious consequences.

So it is important to understand why there were, and still are, of public health concerns.

Although the quality control of medicinal products began in the 19th century, the current guidelines, laws and regulations were mainly adopted in reaction to medical experiments performed before, during and after World War II. For example:

Nuremberg Code 1947: the code is a set of research ethics principles for "human experimentation" established as a result of the unethical medical experiments carried out during World War II by Nazi physicians in the concentration camps.

Declaration of Helsinki 1964: The Declaration is a set of ethical principles adopted by the World Medical Association (WMA) in 1964; the last revision was in 2008. The fundamental principle is respect for human individuals, their right to make decisions regarding their participation in clinical research, before and during the course of the trial. Written informed consent should be obtained from the trial participant or the legal representative. Clinical trials must be scientifically sound and ethically justified, and the rights, safety, and well-being of the participants should prevail over the interests of science and society.

Belmont Report USA, 1979 requiring respect for persons, beneficence and justice; it was prompted in part by problems arising from:

> The Tuskegee Syphilis Study (1932–1972) on African Americans: 400 patients suffering from syphilis were followed, but never received treatment, were not informed about the risks, did not give informed consent. The study was initiated by the U.S. Public Health Service to investigate the natural progression of untreated syphilis in poor, rural black men who thought they were receiving free health care from the U.S. government.
>
> The Willowbrook study, between the mid-50s and up to 1970, this study on hepatitis A was carried out with disabled children. Its aim was to assess the disease in an untreated population and later to evaluate the effect of gamma globulin. The children were intentionally inoculated with the hepatitis virus.

Pharmacovigilance: systematic safety reviews of pharmaceutical products mainly started after the 1960' Thalidomide tragedy. One of the first drugs recognized to cause birth defects in humans. Around 12,000 children were born, with deformities, such as phocomelia which syndromes are undeveloped limbs and absent pelvic bones. Currently the drug is used in the treatment of some cancers and HIV-infected patients.

Today, pharmacovigilance is a worldwide recognized concern and all health care professionals must contribute to ensure the safety profile of medicinal products whether they are marketed or not.

The U.S. Food and Drug Administration (FDA) established regulations for clinical research in 1980, called "Code of Federal Regulations, title 21, part 50 (protection of human subjects)".

RECENT ISSUES

Although, there are many guidelines and regulations in medical research, we are still facing ethical and scientific issues in clinical trials. Some recent ones are:

- In 2005, the VIOXX cases: soon after marketing authorization was granted, the drug was withdrawn from the market because of increased risk of heart attack and stroke associated with long-term, high-dosage use. The data were very controversial and thousands of patients filed lawsuits against the company over adverse cardiovascular events associated with the use of the drug.
- In 2006, the TeGenero case: a phase I trial in healthy volunteers testing a humanized monoclonal antibody reported that the 6 healthy volunteers who had received the drug experienced multiple organ failure and general inflammatory reaction (also known as “cytokine storm”) leading to permanent disability. Some experts stated that the trial design was inappropriate (all subjects were treated almost at the same time). In addition the company was not covered by adequate trial insurance. The company argued that REC and Health Authorities did approve the protocol. This case gave rise to major changes concerning the entry-in-to-man or first-in-man clinical trials in 2007.
- In 2009, the Mediator case: a drug that received marketing authorization in 1976 was withdrawn from the market in 2009 after several years of safety alerts by consumers and physicians, the first one being reported in 1997. The extensive off-label use caused unexpected severe to lethal cardiotoxicity that was down-played by the marketing authorization holder. In addition, there were reports of important conflicts of interest at all company management levels.

6.1 Historical Development of Reference Documents used in Clinical Trials

6.1.1 Codes and declarations

1947
: Nuremberg Code

1948
: Universal Declaration of Human Rights (United Nations)

1964
: Declaration of Helsinki (World Medical Association - WMA), regularly reviewed

1974
: Institutional Review Board (In the United States, IRBs are governed by Title 45 CFR (Code of Federal Regulations) part 46. These regulations implement provisions of the National Research Act of 1974 defining IRB

1979
: Belmont Report (USA): created by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (respect for persons (autonomy), beneficence and justice)

1997
: Universal Declaration on the Human Genome and Human Rights (UNESCO)

2000
: Guidelines for Ethics Committees (World Health Organization)

2002
: International Ethical Guidelines for Biomedical Research involving Human Subjects (Council for International Organizations of Medical Sciences – CIOMS)

2008
: International Ethical Guidelines for Epidemiology Studies. CIOMS Geneva, Feb 2008.

6.1.2 Laws and regulations related to GCP in clinical research

1931
: U.S. Food & Drug Administration 21 Code of Federal Regulations (21 CFR), Parts 11, 50, 54, 56, 312, 314

1989
: Japanese GCP law

1989
: French Loi Huriet

1991
: European Union (EU) – Good Clinical Practice (GCP) guideline

1992
: Swiss Federal Act on Data Protection (status of Jan 2011, doc. 235.1)

1994
: WHO - GCP guideline (the guideline was developed to be applied for registration clinical trials)

1995
: EU – Protection of individuals with regards to the processing of personal data and on the free movement of such data (EU 95/46)

1996
: ICH-GCP E6 guideline (the guideline was developed to be applied for phase I-III pre-registration clinical trials)

2001

Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products 2004

EU Volume 10 Clinical Trials Guidelines and Legislation

6.1.3 Standards and guidelines

- Ethical guidelines (WHO, CIOMS)
- Good Clinical Laboratory Practice (WHO 2009)
- Good Clinical Practice (ICH-E6 GCP)
- Safety reporting: ICH E2A-F
    - Periodic Safety Update Report (PSUR) for marketed products ICH-E2C(R2)
    - Development Safety Update Report (DSUR) ICH E2F
- Adverse events (CIOMS) for products tested in clinical trials

The adoption of those rules and regulations has certainly contributed to improve the protection of research participants during the last decades. Yet, in view of this extensive and complicated set of rules and standards, one should keep in mind this statement from Jay Katz: «Taking as a point of departure the ten “basic principles” set forth by the Nuremberg judges, numerous attempts have been made to propose “improved” codes of ethics to guide medical research. The proliferation of such codes testifies to the difficulty of promulgating a set of rules that does not immediately raise more questions than it answers.» (The Education of the Physician-Investigator, *Experimentation with Human Subjects*, Paul E. Freund (ed.), The Deadalus Library, 1969).

It may be worth looking for alternatives instead of producing more rules and regulations. Too many standards may not be in the best interest of the research participants as they dilute the goals of the regulatory framework. The participants’ protection would be improved if all stakeholders would rather concentrate on the basic principles of research ethics and what it means for their own responsibilities. In case of doubt when interpreting any of those rules, a simple and safe way for anyone responsible is to adopt the interpretation that would guarantee the participant’s best protection.

6.2 ICH Approach

ICH stands for *International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*. It consists of regulatory authorities and pharmaceutical industry representatives of Europe, Japan and the USA (collectively known as the tripartite or ICH region). ICH's mission is to ensure that safe, effective, and high quality medicinal products are developed and registered in the most resource-efficient way.

International Council for Harmonization overview of guidelines originally developed by Prof JM Husson, University of Lyon, France and adapted with his permission. Each guideline covers a specific topic and bears a number (i.e. E2: safety in clinical trial; E6 GCP, etc.)

In summary, the primary aim of ICH-GCP is to remove redundancy and duplication of clinical trials and to produce a single core clinical trial package in a common technical registration dossier for regulatory authorities to facilitate the mutual acceptance of clinical data.

To reach its goals, ICH has developed guidelines that are intended to be globally accepted for bringing medicinal products on the markets:

- **Q:** Quality: related to pharmaceutical and chemical quality assurance (Good Manufacturing Practice - GMP).
- **S:** Safety: related to *in vitro* and *in vivo* (animal studies) pre-clinical studies.
- **E**: Efficacy: related to clinical studies in human subjects, (E1-15, E6: GCP) (Safety reporting E2 belongs to this category).
- **M:** Multi-disciplinary: cross cutting topics (M1-M5) (MedDRA dictionary belongs to this category).

Although ICH guidelines were developed for pre-registration clinical activities (phase I-III), today ICH standards must be applied in all phases of drug development (phase I to IV, bioavailability, and bioequivalence studies). Although clinical trials may be performed for registration purpose outside the ICH region, it is highly recommended that ICH-GCP quality standards are applied to those trials, this will ensure the protection, safety and well-being of the trial participants.

GCP does NOT apply to animal studies and is limited in non-interventional studies in humans (see sections 3.1-3.2).

6.2.1 Good Clinical Practice: what is it?

Good Clinical Practice (GCP) is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

6.2.2 Good Laboratory Practice: what is it?

Good Laboratory Practice (GLP) refers to a quality system of management controls for animal laboratory research and organizations to achieve uniformity, consistency, reliability, reproducibility, and quality, of non-clinical safety tests

Although GLP has been designed for animal laboratory studies, GLP needs to be implemented in clinical trials when Hospital or Laboratory performing diagnostic tests should be certified or accredited by a controlling body (*USA: Clinical Laboratory Improvement Amendments (CLIA)*).

While **Good Clinical Laboratory Practice** (GCLP) is not legally compulsory, the following is important to know:

- Since 2008, EU Inspectors are using guidelines for the conduct of GCP inspections that include **clinical laboratory practice**. The regulatory inspections will include laboratory accreditation status, organization and staff availability, facilities and environment conditions including safety and security (fire, water protection), equipment, materials, and reagents. Trial-related aspects included handling of samples, material and methods (validation status) are also considered.
- In 2009, the World Health Organization (WHO) published the GCLP guidelines targeting research and training in tropical diseases. This guidance identifies systems required and procedures to be followed within an organization conducting analysis of samples from clinical trials in compliance with the requirements of GCP. It provides sponsors, laboratory management, project managers, investigators, clinical research staff and quality assurance personnel with the framework for a quality system in analysis of clinical trial samples, ensuring GCP compliance overall of processes and results. GCLP also covers requirements on method and condition under which human samples are transported from one location to another.

6.2.3 Good Manufacturing Practice: what is it?

Good Manufacturing Practice (GMP) is a set of standards that helps to ensure the highest and safer quality of a product. GMP is regulated in many countries and must be applied by pharmaceutical and medical device companies. Basic concepts include safeguarding the health of the patient as well as producing high quality medicine, medical devices or active pharmaceutical products. Complying with GMP is a mandatory requirement in clinical trials using an Investigational Medicinal Product (IMP).

In the EU, clinical trials must comply with the so-called GMP Annex 13 defining, for instance, the labeling, packaging, shipping, storage condition, and destruction requirements. Annex 16 defines the manufacturing responsibilities in terms of qualified person and batch release.

It must be noted that in the EU, an IMP dossier must be available for non-registered products used in clinical trials.

PART 7. GCP IN CLINICAL TRIALS

Research involving human participants in clinical trials is governed by one of the most detailed legislative frameworks for the protection of human beings.

Worldwide acceptance of clinical data is facilitated by harmonization in the conduct of clinical trials. To help protect the rights, integrity and confidentiality of clinical trial participants, ICH developed a series of guidelines, including the Guideline for Good Clinical Practice (*ICH E6-GCP*). The ICH-GCP guideline provides public assurance that research participants are protected and that clinical trials are conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as well as according to the applicable regulatory requirements.

This training material is based on the current version of the ICH-GCP Guideline E6, the USA - FDA 21CFR, the European Union rules governing medicinal products compiled in the so-called Volumes 9 and 10 and the Swiss laws and regulations related to clinical trials.

7.1 Applicability of GCP

In the ICH region and some other countries, the GCP-E6 Guideline has been incorporated into the national laws and regulations, especially for trial data which support an application for marketing a medicinal product.

The principle of the guideline may also be applicable to other clinical investigations that may affect the safety and well-being of human research participants.

It is strongly recommended that ICH-GCP principles are applied to any interventional clinical research that may have an impact on the safety and well-being of trial participants, even if the trial is conducted outside the ICH-region.

7.2 GCP Principles

In order to avoid the poor and, in some cases, unethical past experiences in clinical research, the principles of GCP ensure that sufficient pre-clinical research is performed before the product is administered to human beings, the clinical trial is only initiated and performed if the anticipated benefits justify the risks, the clinical trial has received prior favorable opinion or approval from the competent Research Ethics Committee (REC), investigators are qualified by education, training and experience, the trial design is scientifically sound, the voluntary consent of the trial participant is obtained, the collected data remain confidential, and the IMP is manufactured according to the highest good manufacturing quality standards.

7.3 GCP Summary

This brings us to end of the first part describing the need, background and applicability of GCP.

In this section, you have learned that **ICH-GCP E6 Guideline** has global acceptance and recognition and following this international ethical and scientific quality standard may provide faster access to medicinal products.

In the next parts, you will learn about the various individuals involved in clinical trials and their roles and responsibilities as per GCP standards.

- WMA Declaration of Helsinki 2008
- ICH-GCP 1996 ⇒ Sect. 1 - 8
- EU The rules governing medicinal products ⇒ Volume 9; 10
- EU Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states. Annex II Clinical laboratory, May 2008.
- EU Volume 4 Good Manufacturing Practices Annex 13: manufacture of investigational medicinal products, 2003
- EU Annex 16 to the EU Guide to GMP: Certification by a qualified person and batch release, 2002
- WHO Good Clinical Laboratory Practice (GCLP) 2009
- US 21-CFR Parts 50; 54; 56; 312, 314
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 10

PART 8. RESEARCH ETHICS COMMITTEE (REC)/INDEPENDENT ETHICS COMMITTEE (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)

8.1 Foreword

While in different jurisdictions the nomenclature (REC/IEC/IRB) may be defined by law; the corresponding committee, investigator and sponsor obligations may vary in detail, the overall responsibilities of the REC with respect to review, approval and ongoing monitoring of clinical research can be summarized in a consolidated approach.

For the purpose of this course, REC will be used for either Research Ethics Committee, or Independent Ethics Committee or Institutional Review Board.

8.2 Reminder

The REC performs an independent assessment of the **scientific** and **ethical** aspects of experiments before the clinical trial starts. The role and responsibilities of the REC, as well as systems and processes under which REC works, are covered in detail in Modules 1 and 2.1 of the TRREE Training program.

It should be reminded that the roles and responsibilities of the REC are:

- **before** the clinical trial starts: reviewing the clinical trial documentation, assessing the investigational site facilities and investigator's competence, as well as evaluating the organization of the clinical trial in order to decide whether to give a favorable opinion before the first participant is recruited in the trial.
- **during** the course of the clinical trial: reviewing any protocol amendments or serious and/or unexpected adverse drug reactions which are likely to affect the safety of the trial participants.
- **continuing** review: each ongoing trial should be reviewed at least once a year. They may be more frequent if the degree of risk to participants warrants it.
- **at the end** of the clinical trial: reviewing the clinical trial summary report.

8.3 REC Record Keeping: Variations in Rules and Laws

RECs must archive the clinical trial documents as well as their own working documents (e.g. agendas, minutes of meetings, lists of membership, SOPs, annual reports, etc). There is an important variation in Rules and Laws regarding the retention period, so the table below provides you with archiving information in some regions. You need to check what are your local laws and regulations regarding records keeping and archives.

Topic	ICH	EU	USA	Switzerland
Retention time	3 years after completion of the trial and must be available upon request from regulatory authority *ICH GCP 3.4*	at least 3 years after completion of the trial or longer if legally required *EU Directive 2005/28/EC Art 6*	at least 3 years after completion of the research and must be accessible for inspection *21 CFR 56.115*	10 years after completion or definitive discontinuation of the trial *Ordinance on Clinical trials, Art. 33*

In summary; the main responsibilities of the REC are to safeguard the rights, safety and well-being of all clinical trial participants by continuously reviewing the trial progress and assessing the ongoing trial documents. An experiment can start only when the REC has given a favorable opinion or provided a positive approval.

- ICH-GCP 1996 ⇒ Sect. 3; 3.3; 3.4
- EU Directive 2001/20/EC ⇒ Art. 6 - 8
- EU Directive 2005/28/EC ⇒ Art. 6
- US 21-CFR Part 56 – Protection of human subjects ⇒ Sect. 56.101 – 56.124
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9 - 12; 33
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 45 - 55

PART 9. INVESTIGATOR

The investigator is the person responsible for the conduct of the clinical trial at a trial site (*ICH 1.34; EU 2001/20/EC Art 2 (f); US 21 CFR 312.3; Swiss Ordinance on Clinical Trials, Art 5, lit c*).

If the trial is conducted by a team, then the responsible leader of the team will become principal investigator (PI). Other members of the team may be designated sub-investigators.

9.1 Be an Investigator

To be an investigator you must fulfill a number of criteria that each sponsor will have to check before you can participate to a clinical trial. It is the responsibility of the sponsor to ensure that you and your investigational site work according to GCP and the domestic laws and regulations.

In case you are also the sponsor of the clinical trial, you will have both the responsibilities of the investigator and those of the sponsor.

Before the trial starts, your role as an investigator requires you to provide the sponsor with all the necessary information regarding your qualifications and the suitability of the site to handle the trial. You also have to ensure that relevant information is made available to you and that all agreements are in place before the trial starts.

- **Qualifications:** To demonstrate that you are suitable to assume the responsibility for the proper conduct of a trial, you should provide evidence of your:
    - education
    - training, including GCP training
    - experience in the disease area and in clinical research

in the form of an up-to-date curriculum vitae (CV) and other documentation that may be also requested by the REC and the regulatory authorities. There are countries (e.g. Switzerland, USA), defining the curriculum for GCP training level that any investigator or sub-investigator should have received.

Time: To demonstrate that you have sufficient time to conduct and complete the trial.**Access to participants:** To demonstrate the feasibility of acquiring the number of participants needed for the proposed trial.**Availability of staff:** To have a sufficient number of qualified staff available for the duration of the trial.**Facilities:** To have access to adequate facilities (e.g. laboratories, pharmacy, cool rooms, equipment, adequate storage for the clinical trial material and the IMP as well as safe storage of confidential data of trial participants) for conducting the trial. Equipment must be suitable, available, maintained and calibrated, and be in working order.

As an investigator you also should be thoroughly familiar with all the information provided by the sponsor before a trial starts, such as the protocol, the investigator’s brochure and other trial-related documents.

There should be a contract between you or your institution and the sponsor. The contract must be signed by both parties before the trial starts. You must conduct the trial in compliance with the approved protocol agreed to by all parties, GCP and the applicable regulatory requirements.

As an investigator you should:

- ensure or obtain ethical clearance from the REC
- ensure or obtain regulatory authorization, if locally applicable
- report all serious adverse events (SAEs) to the sponsor as described in the protocol. In addition, some countries require that the investigator reports trial-related SAEs to regulatory agency independently of the sponsor obligations. All trial-related unexpected SAEs must also be reported to the REC.
- permit monitoring, auditing and inspection by the appropriate regulatory authorities
- give the monitor, auditor, REC or regulatory authority direct access to any trial-related records upon request

- ensure that trial documents are kept for the period of time required by your institution and your country regulations (see also ICH-GCP 5.1.4).

- ICH-GCP 1996 ⇒ Sect. 4.1.2; 4.1.3; 4.2.1; 4.2.2; 4.2.3; 4.5.1; 4.9.7
- EU Directive 2001/20/EC ⇒ Art 2 (f)
- US 21-CFR Part 312 - Investigational new drug application ⇒ sect. 312.3; 312.53 (a)(c); 312.60
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 8

9.2 Investigational Site Organization

The investigational site must have adequate facilities, services and resources to perform the clinical trial. Therefore, the site must provide:

- **Medical care of trial participants:**
  - A qualified physician (or dentist) who is the investigator for the trial should be responsible for medical (or dental) decisions and enrolment of participants in the clinical trial.
  - Emergency room and equipment must be available.
  - Availability of trial staff to participants and/or suitable arrangements for immediate access to care
- **Site staff training**

  Training the investigational staff members is the responsibility of the investigator.

  - All investigational team members should be fully informed about: the protocol, the trial procedures, the Investigational Medicinal Product (IMP), their duties and function in the clinical trial. When changes are made to the protocol or a specific trial-procedure, the investigator is responsible for training his/her team on the changes.
  - Every investigational team member must be trained on GCP. In some countries, the content of GCP courses is regulated by national laws (see also section 9.1. above).
  - Staff training must be documented. A Training Certificate must be available and must mention the duration of the training, trainer's name, accreditation institution (when applicable), location as well as the name of the person who took part in the training.
- **Delegation:**
  - The investigator should maintain a list of appropriately qualified persons to whom he/she delegates significant trial-related duties. The list must be current. The list must contain the exact duty(ies) as well as the start and end date of each staff member's involvement.

- ICH-GCP 1996 ⇒ Sect. 1.34; 4.1.5; 4.2.4; 4.3.1
- EU Directive 2001/20/EC ⇒ Art. 1
- US 21-CFR Part 312 - Investigational new drug application ⇒ Sect. 312.60 – 312.62; 312.64; 312.66; 312.68; 312.69
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 8
- Swiss GCP training programs investigator and co-investigator: Anforderungen an die Ausbildung von Co-Prüfern, Hauptprüfern und Sponsor-Prüfern im Rahmen von klinischen Versuchen mit Heilmitteln – Beilage 1, 2

9.3 Pre-trial Processes

In the pre-trial phase, all the procedures and processes are put in place and relevant information with regard to the conduct of the trial is made available to the concerned parties.

As an investigator, it is your responsibility to share the necessary information and submit the relevant documentation required from you. Contract and financial agreements must be available before the trial starts.

9.3.1 REC Approval/Favorable Opinion Before the Trial Starts

- In principle, the investigator communicates with the REC in accordance with domestic laws and regulations (see module 2.1 for details). In clinical trials conducted under the EU Directives, it is the sponsor's responsibility to ensure that the clinical trial has been approved by the REC before the trial starts (*EU Directive 2001/20/EC Art 9*).
- Before a trial begins, the investigator must obtain written and dated approval/favorable opinion from the REC for the protocol, written informed consent form, participant recruitment procedures and any other written information to be provided to potential participants.

- ICH-GCP 1996 ⇒ Sect. 4.4.1
- EU Directive 2001/20/EC ⇒ Art. 9
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.66
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9.
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 45, 47

9.3.2 Finances

- The financial aspects of the trial should be documented in an agreement between the sponsor and investigator/institution. A financial disclosure may be required in some countries (e.g. USA Form 3455).

- ICH-GCP 1996 ⇒ Sect. 4.9.6
- EU Directive 2001/20/EC ⇒ Art. 6.3 (j)
- US 21-CFR Parts 54, 312 ⇒ Sect. 54.1-54.6; 312.5 (c)(4)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9 al. 2 lit. d; 10 al. 2 lit. m

9.3.3 Trial Participant

The essential elements of the informed consent form, the informed consent documents and the

informed consent process are covered in detail in Module 3.1.

As an investigator, you must ensure that before the trial starts, you have the final version of the informed consent form and participant information sheet and that all those documents have been approved by the REC.

It is also your responsibility to have access to and may expect to be able to enroll sufficient numbers of eligible participants.

- ICH-GCP 1996 ⇒ Sect. 4.8
- EU Directive 2001/20/EC ⇒ Art. 3.2 (b); 4 (a); 5 (a); 6.3 (g)
- US 21-CFR Part 312-Investigational new drug application ⇒ 312.60
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 6, 9
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 16

9.3.4 Investigational Medicinal Product

- **Investigational Medicinal Product (IMP) knowledge:** The investigator should familiarize him/herself with all the information given about the IMP in different documents (e.g. the protocol, IB, other IMP specific publications.)
- **The supply of the IMP** is given only once the investigator has provided all required documentation to the sponsor (i.e. CVs, laboratory normal ranges, list of staff members) and the REC and regulatory authority have approved the clinical trial
- **IMP dispensing duties:** The investigator may be allowed or required to assign some or all of the accountability for the IMP to a pharmacist at the trial site
- **IMP shipping records:** The investigator or other designated individual at the trial site should record the delivery of the IMP and should maintain detailed records about the administration of the IMP throughout the trial
- **IMP Storage:** The investigator should comply with the sponsor's instructions and any other regulatory requirements relating to the storage of the IMP
- **IMP data** on the formulation, safety, indication, contra-indication, efficacy, dosage, route and schedule of administration and duration of treatment are well defined in the approved protocol.

- ICH-GCP 1996 ⇒ Sect. 4.1.2; 4.6.2-4.6.4; 5.14.2
- EU The rules governing medicinal products ⇒ Volume 4, Annex 13: Manufacture of investigational medicinal products, 43-55 (Shipping-Return and Destruction paragraphs)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.59; 312.62
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products⇒ Art. 14, al. 1, lit. a
- Swiss Ordinance of 17 October 2001 on the Authorizations in the field of medicines ⇒ Annex 1

9.3.5 Investigator Site File (ISF):

An ISF should be established at the investigational site or institution at the beginning of the trial and maintained during the entire trial period. The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules by giving each participant a unique identifier in lieu of the participant's name.

The ISF should be organized in accordance with the list described in ICH-GCP 8 before, during and at the end of the clinical trial. In some countries, the ISF may have to be organized as per local regulatory requirements.

Any electronic filing system or e-records must be used within an adequate document management system that is validated and the access limited to assigned site staff, must be protected by password and specific identification. Adding or changing e-data must be controlled by an audit trail. Computerized systems used in clinical trials are regulated in the entire ICH region and include "Creation, modification (audit trail), maintenance, archiving, retrieving or transmitting of clinical data"

- ICH-GCP 1996 ⇒ Sect. 5.5.3; 8; 8.1
- EU Directive 2005/28/EC ⇒ Art. 5
- EU Directive 95/46/EC on data protection
- EU Recommendation on the content of the trial master file and archiving, July 2006
- EU Directive 1999/93/EC on Community Framework for Electronic signatures
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 11: Computerized systems
- US 21-CFR Part 11 ⇒ Sect. 11.10; 11.30; 312.62
- US Guidance for Industry Computerized Systems used in Clinical Investigations. Publ. US Dept Health and Human Services FDA May 2007
- US FDA guidelines on General principles of process validation, 1987
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 14
- Swiss Federal Act of 19 June 1992 on Data Protection

9.4 During the Trial

As an investigator, you and your team have a major role to play while the trial is in progress. It is your responsibility to ensure that the conduct of the trial is in accordance with the protocol and approved documents and that trial-related documentation is maintained accurately.

Before treating the first participant, you must ensure that the following systems, processes and documents are in place. This includes, but is not limited to:

- a signed contract with the sponsor
- an approved REC protocol
- an approved informed consent form and participant's information sheet
- blank case report form
- IMP in sufficient quantity, adequate storage condition
- sample shipment procedure, if applicable
- clinical trial relevant equipment such as ECG machine, fridge and freezer that are calibrated and properly maintained
- an up-to-date list of personnel to whom tasks are delegated
- documentation that the trial personnel have been trained to assume their tasks and responsibilities for the proper conduct of the trial. Training must include GCP, protocol and trial-specific requirements.
- have access to sufficient number of eligible volunteers/patients
- have access to emergency facilities

You also have to ensure that all rules and regulations regarding the informed consent form and trial participants are followed (see Modules 2.1 and 3.1).

- ICH-GCP 1996 ⇒ Sect. 4.5; 4.8
- EU: no specific references, apply ICH-GCP
- US 21-CFR Parts 50, 312 ⇒ Sect. 50.20; 50.23; 50.24; 312.60; 312.62
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

9.4.1 Protocol deviations/changes

As an investigator, you should conduct the trial in strict compliance with the protocol. You should obtain a written **agreement** from the sponsor and **documented approval** from the REC before implementing any deviations from, or changes of, the original approved protocol. This requirement does not apply if a trial participant needs immediate protection from a hazard or if the change involves only logistical or administrative aspects of the trial such as change of telephone number or monitor.

If any deviation is made, you should explain and document it, and communicate details of the change to the Sponsor, the REC, the monitor, and if applicable to the regulatory authorities. You should keep the correspondence and documentation of the case in the ISF.

- ICH-GCP 1996 ⇒ Sect. 4.5.2; 4.5.3; 4.5.4
- EU Directive 2001/20/EC ⇒ Art 10
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.30
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 19
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 45 al. 3

9.4.2 Communication with the REC

- During the trial, the investigator should provide the REC with all documents to be reviewed. This may include, but is not limited to, updated safety information, any new version of the IB, a protocol amendment, a new version of the informed consent form or any other important information concerning the product under clinical research. Progress reports issued by the investigator should be sent to the REC at least annually.
- The investigator should also comply with the applicable regulatory requirements regarding safety reporting as **unexpected, serious adverse drug reactions** may have to be reported to the REC and regulatory authority by the investigator. Section 12 of this module covers the Safety Reporting requirements.

- ICH-GCP 1996 ⇒ Sect. 4.4.2; 4.4.3; 4.10.1; 4.8.2; 4.9.7;4.11.1
- EU Directive 2001/20/EC ⇒ Art. 16; 17
- US 21-CFR Parts 56;312 ⇒ part 56, Sect. 312.66
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 19; 20; 23; 24
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 46

9.4.3 Informed Consent

The entire Informed Consent concept and requirement is detailed in ICH-GCP section 4.8 and is covered in Module 3.1 of the TRREE Training program.

It must be remembered that:

- full information should be provided to the trial participants by the investigator in a personal talk
- prior to participation in a trial, the written informed consent form should be signed and personally dated by the participant or legal representative.
- a copy of the completed informed consent form must be provided to the trial participant, and one copy must remain in the source document.
- the participant source document such as the hospital records must mention when the participant signed their consent to participate in the trial.
- if new information could affect a participant's willingness to continue in a trial, the participant or their representative should be given the information in a timely manner and a new informed consent form must be completed and signed.
- the investigator should inform the participant's family doctor of their participation in the trial, provided the participant gives permission (ICH GCP 4.3.3).

- ICH-GCP 1996 ⇒ Sect. 4.3.3; 4.8; 4.8.8; 4.8.11; 8;
- EU Directive 2001/20/EC ⇒ Preamble (16); Art 2 (j); 3-5
- US 21-CFR Part 50-Protection of human subjects ⇒ Sect. 50.20; 50.27
- Swiss Federal Act of 15 December 2000 on Medicinal Products and Medical Devices ⇒ Art. 54 - 56
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 6, al. 2
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 7; 16 - 18; 21 – 24; 31 – 34; 36; 39

9.4.4 Investigational Medicinal Product

In addition to the information regarding the IMP described in section 9.3.4 (before the trial starts); during the course of the clinical trial, the **investigator remains responsible** to ensure that:

- the sponsor has provided sufficient quantity of IMP to treat the participants for the entire duration of the trial.
- the trial participants are correctly informed on the administration of the IMP for the duration of the trial and, in case the participants take the trial medication at home, a periodic check is done to ensure that the participant continues to use the drug correctly.
- the trial randomization procedures are correctly followed and the randomization code is only broken in accordance with the protocol or in case of an emergency situation.
- there is a permanent check of the IMP records and storage conditions. IMP information should be accurate and records must refer to dates (received by the sponsor, delivered to the participants, returned by the participants), quantities, batch numbers, expired dates, IMP code, and participant identification code.

- ICH-GCP 1996 ⇒ Sect. 4.6.1-4.6.6; 4.7; 5.14.1
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 13: Manufacture of investigational medicinal products
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.59; 312.62(a)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

9.4.5 Adverse Event and Serious Adverse Event

The safety reporting system and process are described in detail in this module, Section 12. Variations in safety reporting laws and regulations may be country-dependent but the basic principles remain the same for the investigator.

It must be noted that:

- Serious Adverse Event (SAE) occurrences should be reported immediately to the sponsor:
    - using participants' unique code identification rather than names,
    - information must be followed promptly by a written report that complies with regulatory requirements.
- The REC must also require immediate notification, especially in case of trial-related deaths/life-threatening events as well as unexpected adverse drug reactions.
- The investigator should also comply with all specific reporting requirements identified in the protocol, such as:
    - adverse events (AEs) or laboratory abnormalities being critical to safety evaluations
    - deaths, for which the sponsor and REC may request additional information (e.g. autopsy reports)
    - requirements made by an Independent Data Monitoring Committee (IDMC)
- In case the investigator is also the sponsor of a clinical trial, it is their responsibility to also report all Suspected Unexpected Serious Adverse Reactions (SUSARs) to Health Authorities and the REC.

- ICH-GCP 1996 ⇒ Sect. 4.11
- EU Directive 2001/20/EC ⇒ Art 2 a), m)-p); 16.3; 16.4; 17.1 a)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.32; 312.56; 312.60
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art 20; 22; 23
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 46, al. 1 lit b), c)

9.4.6 Premature Discontinuation of the Trial

If a trial ends prematurely or is suspended, for any reason, the investigator should inform the participants, arrange for a final evaluation visit and follow up of the participants, and inform the REC (and if required, also the regulatory authorities).

A final report should be written and submitted to the REC after the discontinuation of the trial. In the EU this should be done within 6 months.

- **Investigator termination:** If the investigator decides to terminate or suspend a trial, the sponsor and REC should both be informed promptly and given a written explanation for the termination.
- **Sponsor termination:** If the sponsor decides to terminate or suspend a trial, the investigator should inform the institution, where applicable, and the REC, and provide the latter with a written explanation.
- **REC termination:** If the REC terminates or suspends its approval of a trial, the investigator should inform the institution, the health authorities where applicable, and the sponsor, and provide the latter with a written explanation.

- ICH-GCP 1996 ⇒ Sect. 4.12
- EU Directive 2001/20/EC ⇒ Art 12
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.44; 314.153
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 21
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 46 al. 1 lit a)

9.4.7 Investigator Site File during the Course of the Trial

- The investigator should maintain complete and accurate trial documents in a safe place (fire and water protected).
- Special attention should be paid to updated documents (e.g. investigator's brochure, protocol amendments, new informed consent forms, new safety information) and CVs of new staff members.
- Attention should be paid to any e-records that must be used within an adequate document management system that is validated and the access protected by password and specific identification. Adding or changing e-data must be controlled by an audit trail. Maintain a security system that prevents unauthorized access to the data
- The investigator should take measures to prevent accidental or premature destruction of these documents.

- ICH-GCP 1996 ⇒ Sect. 4.9.4; 5.5.3; 8.3
- EU Directive 2001/20/EC Article 15(5)
- EU Directive 2005/28/EC Article 16
- EU Recommendation on the content of the trial master file and archiving, July 2006
- EU Directive 1999/93/EC on Community Framework for Electronic signatures
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 11: Computerized systems
- US 21-CFR Parts 11; 312 ⇒ Sect. 11.10; 11.30, 11.70;312.62(b)
- US Guidance for Industry Computerized Systems used in Clinical Investigations. US Dept Health and Human Services FDA May 2007
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art 25

9.4.8 Investigator during Trial Summary

In this section, you have learned that it is the investigator's responsibility to:

- Conduct the trial in accordance with the protocol and approved documents.
- Ensure that trial-related documentation is maintained accurately and as per requirements.
- Ensure correct storage and dispensing of IMP
- Provide direct access to any requested trial-related records upon the request of the monitor, auditor, REC or regulatory authority and keep them informed of deviations and updates at all times.
- Complete all formalities with regard to the informed consent form and trial participant as per requirements.
- Maintain the essential documents as per requirements in the event of termination or suspension of the trial.
- Ensure correct storage and dispensing of IMP and instruct the participant in the correct way to use the drug.
- Ensure the safety and well-being of the trial participants throughout their involvement

9.5 Post-Trial Processes

In the post-trial phase, all the final documentation, submissions and closures take place in compliance with standards outlined in the pre-trial phase.

As an investigator, you have a very important part to play in the post-trial phase. You are also accountable for the IMP and you have to submit final reports.

9.5.1 Investigational Medicinal Product

The investigator's records must contain documentation to enable a full reconciliation of the trial medication at the site. This should include the amount (*ICH-GCP 4.6.3*):

- delivered to the site
- dispensed to participants
- returned from the participants to the investigator (if applicable)
- returned from the investigator to the sponsor
- disposed of: dates, quantities, batch or series numbers and expiry dates should all have been recorded
- certificate of destruction, if done at the investigator site

9.5.2 Communication with the REC and Regulatory Authorities

When the trial is completed, as an investigator you should:

- provide the REC with a summary of outcomes (Final Report) (*ICH-GCP 4.13.*)
- when applicable, provide the regulatory authorities with any reports required (the sponsor should prepare and provide the Clinical Trial Report to satisfy applicable regulatory requirements (*ICH-GCP 4.13.*)).

9.5.3 Essential Documents and Archives

9.5.3.1 Principles

Essential documents are documents serving to demonstrate the compliance of the sponsor, investigator and monitor with the standards of GCP and applicable regulatory requirements.

The investigator should maintain complete and accurate trial documents in a safe place, as specified in section 8.4 of the ICH-GCP Guideline and as required by the regulatory authorities (*ICH-GCP 4.9.5.*). The investigator shall archive the trial documents and all related source documentation according to their institution's standard operating procedures.

9.5.3.2 Records keeping: Variations in Rules and Laws

There is an important variation in Rules and Laws regarding the duration of clinical trial document retention. The table below provides you with archiving information in some regions. You need to check your local laws and regulations regarding records keeping and archives.

Topic	ICH	EU	USA	Switzerland
Retention time	Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.	at least 5 years after completion of the trial or longer where so required by national regulation *EU Directive 2005/28/EC Art. 17*	2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. *21 CFR 312.62c*	at least 10 years after completion or definitive discontinuation of the trial using an IMP. 15 years for medical devices *Swiss Ordinance on Clinical Trials Art. 25*

ICH GCP 4.9.5

- ICH-GCP 1996 ⇒ Sect. 4.6.3; 4.9.4-5; 5.5.3; 5.5.12; 8.3
- EU Directive 2001/20/EC ⇒ Art. 15 (5)
- EU Directive 2005/28/EC ⇒ Art. 16; 17
- EU Recommendation on the content of the trial master file and archiving, July 2006
- EU Directive 1999/93/EC on Community Framework for Electronic signatures
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 11: Computerized systems
- US 21-CFR Parts 11; 312 ⇒ Sect. 11.10; 11.30, 11.70;312.62(b,c)
- US Guidance for Industry Computerized Systems used in Clinical Investigations. US Dept Health and Human Services FDA May 2007
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art 25

9.5.4 Investigator Summary

This brings us to the end of the Investigator’s Role and Responsibilities in clinical trials.

In this section, you have learned your role and responsibilities during the entire clinical trial process including the protection of the trial participants, the handling of the IMP, how to maintain your source documents, and what documents need to be kept in the archives.

PART 10. SPONSOR

10.1 Sponsor Definition

A clinical trial sponsor can be:

- a pharmaceutical or biopharmaceutical company,
- a government
- an investigator
- a group of investigators
- a non-governmental institution

which takes the responsibilities for trial design, providing the IMP and other trial medication, initiating, managing, and/or financing a clinical trial.

There are variations in the definition of sponsor within the ICH region, especially for clinical trials not initiated by a Pharma or a BioPharma company.

10.1.1 Sponsor-Investigator: Variations in Rules and Regulations

- **In the European Union**, a non-commercial trial can be initiated, managed, conducted and financed by researchers without the participation of the pharmaceutical industry, if the planned trial does not require particular manufacturing or packaging processes.
- **In the US**, "*Sponsor-Investigator*" means an individual who both initiates and conducts an investigation, and under whose immediate direction the IMP is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.
- **In Switzerland**, a sponsor can be any person or organization that takes the responsibility to initiate, manage or finance a clinical trial. If an investigator is also a sponsor, then he/she takes the entire sponsor's responsibility.

- ICH-GCP 1996 ⇒ Sect. 1.53
- EU Directive 2001/20/EC⇒ Preamble (14); Art. 2 (e)
- EU Directive 2005/28/EC ⇒ Preamble 11; Art 7.2
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.3
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 5 lit. b), c)

10.2 Be a Sponsor

Unless otherwise specified, a sponsor does not conduct a clinical trial. The sponsor must implement and maintain quality systems and procedures before, during and at completion of a project to ensure that the trial is conducted and monitored and that data are generated, documented, processed and reported in compliance with the protocol, GCP and regulatory requirements.

Before the trial starts, the sponsor must define the project that will be conducted, who will be involved, the mission of each team member, whether external resources will be necessary, whether external expertise will be valuable for the project, or whether the manufactured IMP is available. The sponsor must also ensure that all ethical and legal requirements are fulfilled in each country where the project will be performed.

- **Project team members:** The sponsor should define, establish and allocate all trial-related duties and functions before the trial starts. In addition, the sponsor must also designate appropriately qualified medical personnel; if necessary, outside consultants may be appointed. The qualified team members, such as biostatisticians, pharmacologists, or physicians, should be involved throughout the entire clinical trial process (from designing the protocol to final clinical trial reports). Each team member must know their function, duties and responsibilities in the project.
- **Contract:** There should be a contract between the sponsor and the investigator(s) and any other third parties that are involved in the clinical trial process (e.g., IMP distribution, safety reporting, monitoring, data management, biometric activities, etc). All contracts must be signed by the parties before their involvement or the tasks start.

The majority of the course of actions to be followed is found in GCP quality standards and regulatory laws and regulations.

- ICH-GCP 1996 ⇒ Sect. 1.17; 1.20; 5.1.1; 5.2;5.3; 5.4.1; 5.5.1; 5.7; 5.18
- EU Directive 2001/20/EC ⇒ Art. 2 (l)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.52
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9 al. 2 lit. k); 14

10.3 Contract Research Organization

A Sponsor may transfer all or part of its trial-related duties to a Contract Research Organization (CRO), but the ultimate responsibility for the quality of the trial resides with the sponsor (*ICH GCP 5.2.1*).

The CRO must apply the same quality, guidelines and regulations as the sponsor.

The relationship between the sponsor and the CRO must be carefully documented in a contract. Any duty or function that is not specifically transferred remains the entire responsibility of the sponsor.

- ICH-GCP 1996 ⇒ Sect. 5.2
- EU Directive 2005/28/EC ⇒ Art. 2 (l)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.52
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9 al. 2 lit. k); 14