ENGLISH VERSION – FINAL VERSION 1.0- 2012-08-27

MODULE 3.2: GOOD CLINICAL PRACTICE

This module is a current and comprehensive guide to the elements and principles of Good Clinical Practice (GCP) quality standards for clinical trials. This module is complementary to Modules 1, 2.1 and 3.1 of the TRREE Training program. Those modules need to be completed prior to beginning this one.

This module delineates the basic GCP and regulatory requirements covering clinical trials on medicinal products for human use. Due to the wide variations in rules and laws within the International Conference on Harmonization (ICH) region and other pharmaceutical markets, each section of the module will provide references to ICH-GCP recommendations, European Union (EU) laws and regulations, United States of America (USA) laws and regulations (in particular the FDA rules) and the Swiss laws and regulations (in particular the Swissmedic rules), setting forth the quality standards for the conduct of clinical trials.

Objectives: At the end of Module 3.2, participants will:

- understand the basic elements of clinical research in general and of clinical trials in particular
- understand the basic elements of GCP in clinical trials
- be aware of and understand the technical terms, language and wording standardized by ICH and regulatory bodies in clinical trials
- be able to identify and put in practice the international quality standards required in clinical trials
- understand the roles and responsibilities of the sponsor (including their third party contractors) and investigators involved in clinical trials. For more clarity, some paragraphs have been repeated in different sections
- be familiar with the regulatory authority requirements in the conducting of clinical trials

Attention: This basic GCP course **is not intended to cover**

- advanced clinical trial methodology
- detailed biostatistics methodology in clinical trials

- disease-oriented clinical trial designs, aims, and approaches
- drug-oriented clinical trial requirements
- additional country-specific conditions

We are also aware that the common vocabulary used by some researchers in biomedical research may differ from the specific GCP terminology. Nevertheless, for the purpose of this module, we intend to comply strictly with the terminology defined in the ICH-GCP guidelines and regulatory documents. This is in-line with our training objective ensuring that the module's participants will have the appropriate expertise with the GCP terminology.

Overview: Module 3.2 has 12 sections including 25 questions. (Three additional sections refer to "list of abbreviations", "glossary" and "references".)

You must get the correct answer before moving ahead. At the end of this module, a certificate is available for participants who get 70% correct answers on their first try.

The use of the words "correct" and "incorrect" to qualify the chosen answer indicates, for some questions, which is the best answer and why. This does not necessarily mean that other answers would never be correct. The questions are intended as a means of prompting and furthering reflection.

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INTRODUCTION TO CLINICAL RESEARCH

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”.

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 7.0

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

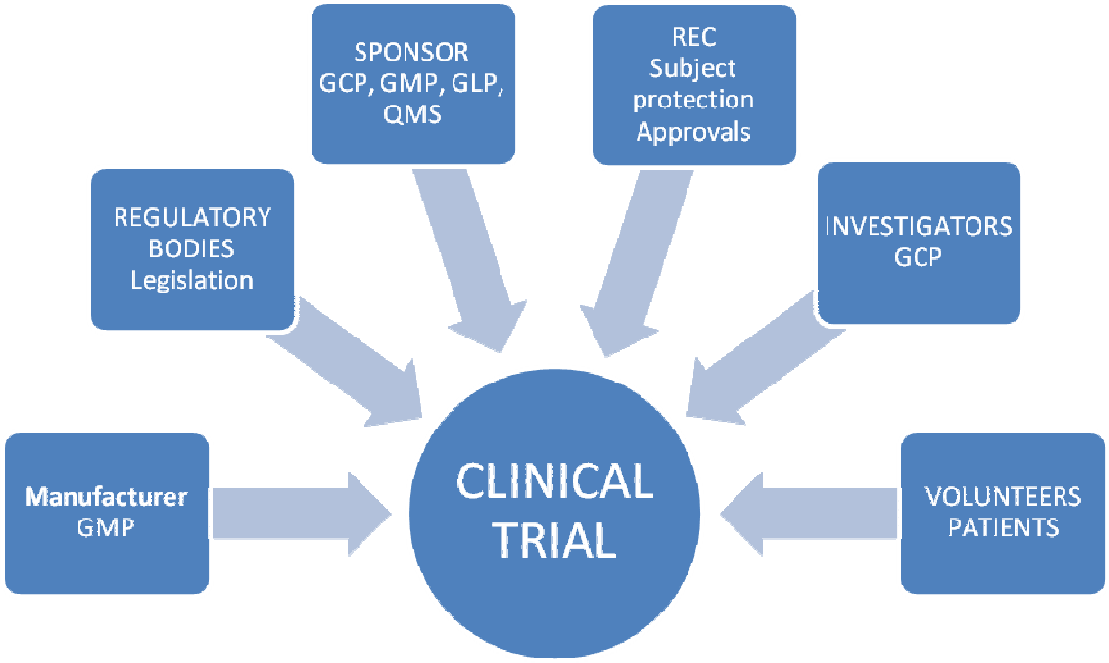
Before initiating clinical trials in humans, the sponsor must compile extensive information on:

- 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.

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.

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. ŧ

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 design has 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

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

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 for Federal Regulations, title 21, part 50 (protection of human subject)".

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 for 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

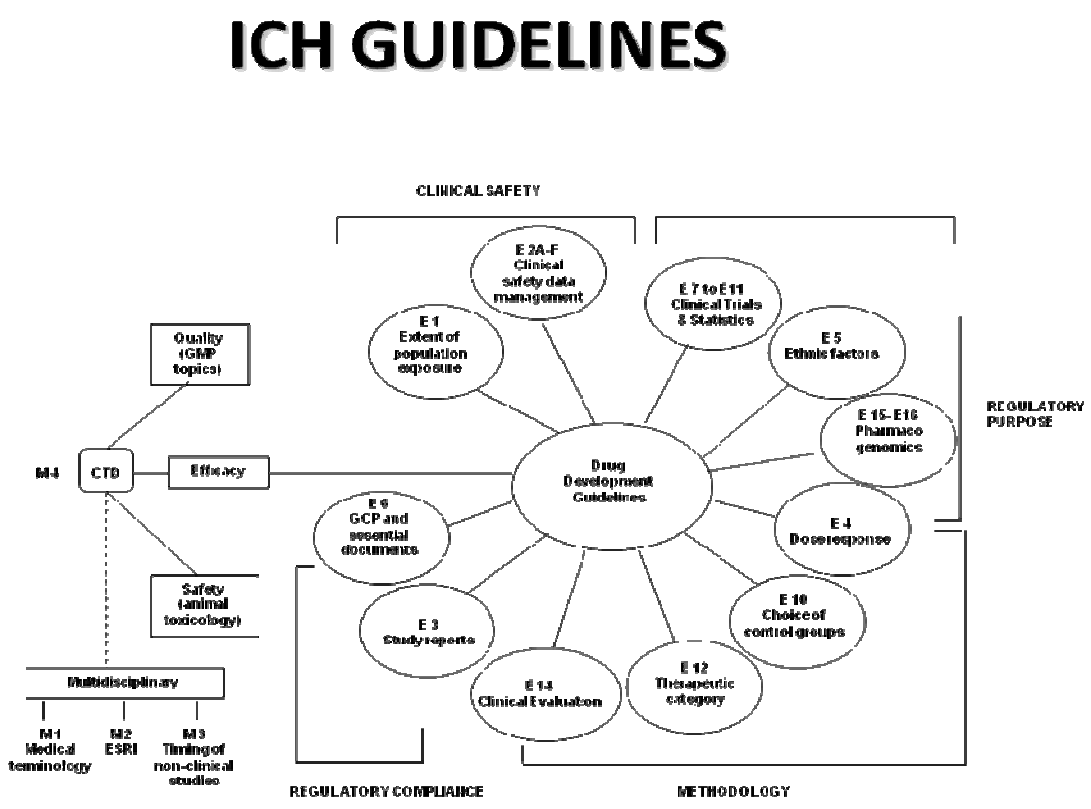
The adoption of those rules and regulations has certainly contributed to improve the protection of research participants during the last decades. Yet, in view of this extensive and complicated set of rules and standards, one should keep in mind this statement from Jay Katz: «Taking as a point of departure 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 alternative 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 Conference on 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 Conference on 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.

7 GCP IN CLINICAL TRIALS

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

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 Records 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

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 8.0 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; 8.0; 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 (ADRs)** 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; 8.0;
- 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 regulatory authorities, if required.

The trial data must be analyzed and a final report should be written within 6 months after the discontinuation of the trial.

- **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	The sponsor should inform the investigator(s), institution(s) in writing of the need for record retention and should notify the investigator(s), institution(s) in writing when the trial related records are no longer needed. *ICH GCP 5.5.12*	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 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.

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.

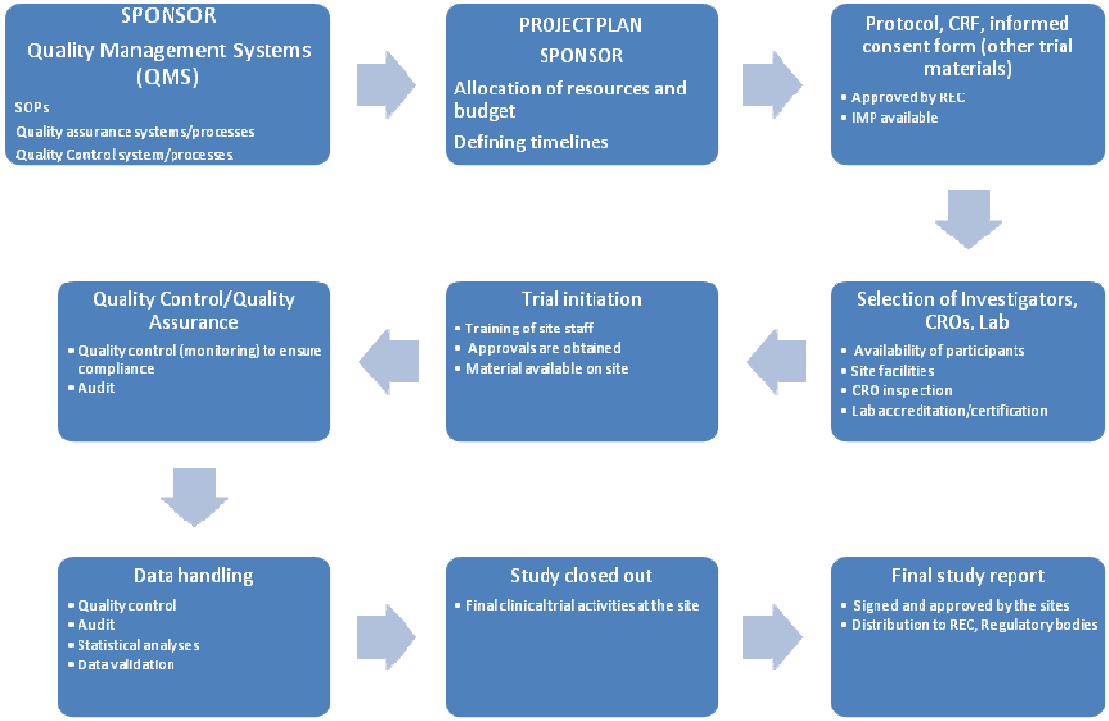
- ICH-GCP 1996 ⇒ Sect. 5.2
- EU Directive 2005/28/EC ⇒ Art. 2 (l)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.52
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9, al. 2 lit. k); 14

10.4 Quality Assurance and Quality Control

ICH-GCP requires that Quality Assurance (QA) and Quality Control (QC) are implemented and maintained during the entire clinical trial process *(ICH-GCP 5.1.1*). To be noted: clinical trial quality assurance is not a regulatory requirement per se. However, sponsors do apply independent audits, quality control and data verifications to determine the compliance with the project set up, their Standard Operating Procedures (SOPs) and the regulatory requirements on quality standards (see also section 11, monitor).

It is good practice that the sponsor develops prospectively within its quality system, pre-defined monitoring and audit plans.

These QA/QC activities may be conducted within the sponsor organization or with external resources. Audit activities must be independent of, and separate from routine monitoring, the trial project or quality control functions.



10.4.1 Standard Operating Procedures

Standard Operating Procedures (SOPs) are guidelines that define detailed, written instructions to achieve uniformity of the performance of a specific function (*ICH GCP 1.55*).

The aim of SOPs and the attached forms or checklists is to simplify the organization and documentation of the clinical trial processes whilst maintaining GCP standards. This also allows an approach of continuous high quality of the project between and within the staff involved in the clinical trial.

SOPs must be tailored to suit the sponsor's needs as long as there is compliance with GCP and regulatory requirements. SOPs should be detailed enough so that a procedure can be correctly carried out in a reproducible manner, but not so specific that they can only be applied to a single clinical trial and then have to be rewritten for the next course of actions.

- ICH-GCP 1996 ⇒ Sect. 1.55; 5.1.1; 5.19.3
- EU Directive 2001/20/EC ⇒ Art. 1
- EU Directive 2005/28/EC ⇒ Art. 1.4; 21.5
- US 21-CFR Part 312-Investigational new drug application ⇒ section 312.56
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

10.4.2 Monitoring

The sponsor should determine what comprises 'adequate' monitoring, taking into account the trials design, objectives, purpose, complexity, endpoints as well as the number of investigational sites and countries (*ICH-GCP 5.18.3*.). It is good practice that the sponsor develops a monitoring plan before the trial starts.

Regulations do not prescribe a specific monitoring technique; in general, there is a need for on-site monitoring before, during and after the trial. The monitor should provide a written report to the sponsor after every trial site visit or trial related communication (*ICH-GCP 5.20.1*).

On-site monitoring visits are done either by a monitor employee of the sponsor or by a third party representative under the sponsor's responsibility. It is the sponsor responsibility to ensure that the investigational site will provide all source documents and access to clinical site files for the purpose of monitoring, auditing and inspections from health authorities.

If the monitoring activities reveal any non-compliance, then the sponsor should act promptly to rectify the situation, even if the monitoring activities are done by a CRO. If there is serious or persistent non-compliance, the sponsor should terminate the investigator's participation in the trial, and notify promptly the regulatory authority (*ICH-GCP 5.20*) and the REC.

Detailed monitoring activities are covered in section 11of this module.

- ICH-GCP 1996 ⇒ Sect. 5.18.3; 5.20
- EU Directive 2001/20/EC ⇒ Art. 2 (l) ; 3.2 a)
- EU Directive 2005/28/EC ⇒ Art. 2.4; 4
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.56
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

10.4.3 Auditing

Clinical trial quality assurance is not required by regulation. However, many sponsors perform independent audits and data verification to determine compliance with trial procedure, SOPs and legal regulatory requirements.

On the other hand, when sponsors perform audits as part of implementing quality assurance they should consider (*ICH-GCP 5.19)*:

- **Purpose**: The purpose of an audit, which is independent of monitoring or quality control functions, is to check compliance with the protocol, SOPs, GCP and the applicable regulatory requirements.
- **Appointment of the auditor**: The appointed auditor should be independent of the trial and appropriately qualified.
- **Audit process**: The audit should comply with the sponsor's written procedures on what and how to audit, the frequency of audits and the form and content of audit reports.

- **Standards**: The sponsor must develop an audit plan and audits are performed against predefined quality standard documents *(ICH-GCP 5.19.3*). The following documents can be used by auditors to perform sponsor, manufacture and/or investigational site audits:
    - Sponsor SOPs
    - Manufacturer SOPs
    - Investigational site SOPs
    - International GCP standards (ICH-GCP)
    - Applicable regulatory requirements (e.g. The rules governing medicinal products in the European Union, volume 10; US 21 CFR)
    - Domestic legal requirements
    - Clinical trial protocol (all approved versions)
    - Computer system validation plan
    - All clinical trial essential documents

The sponsor's audit plan and procedures should take into account:

- whether the trial is pivotal or not or whether the trial will support a registration package submitted to regulatory authorities
- the number of participants in a trial
- the type and complexity of a trial
- any identified problems

The outcomes must be documented in a report and a corrective and preventive action plan must be drawn up, if needed.

The regulatory authorities may request access to the reports, but only in exceptional circumstances (such as in cases of proven fraud).

The sponsor should provide an audit certificate when required by law or regulation, to document that an audit was performed (*ICH-GCP 5.19.3*).

- ICH-GCP 1996 ⇒ Sect. 5.19
- EU Directive 2005/28/EC ⇒ Art. 16
- US 21-CFR Part 314 ⇒ 50.d5(xi)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

10.4.4 Fraud and Misconduct

Good Clinical Practice requires accurate and reliable data. The data should be checked by trial monitors, and independent data monitoring committee and/or health authority inspectors. Although many guidelines and regulations are in place to avoid fraud and misconduct in clinical trials, non-compliance with procedure and trial protocol by an investigator may provide suspected data. Suspected data may or may not be fraudulent. In-depth for cause audit should be

carried out to identify whether the suspected findings are critical and may jeopardize the clinical trial results in general and the security of the trial participants in particular.

Deviations in clinical trials may be due to uncontrolled factors such as toxicity, trial participant's refusal or non-compliance, concomitant disease or early death. **Violations** are deviations from the clinical trial protocol which could have been prevented by the investigator and may affect the final results. **Fraud** can be qualified as deliberate falsification of the data (e.g. generation of false data with the intent to deceive, completion of the CRF with data of non-existent patients or the of use data of dead patients).

Prevention of misconduct comes first by ensuring that the investigational site is adequately trained on the protocol, legal requirements and all procedures that must be followed during the course of the trial. But if serious and repeated misconduct or fraud is detected and confirmed then the sponsor must consider applying a corrective and preventive action. Serious and repeated non-compliance of an investigational site should be reported to the REC and Health Authorities.

10.5 Pre-Trial Process

10.5.1 Documents

In clinical trials, all documents, including e-documents, must be handled within an adequate document management system, to ensure the adequacy of the versions, dates, languages used, and length of each document. Computerized systems used in clinical trials are regulated in the entire ICH region and consist of “Creation, modification (audit trail), maintenance, archiving, retrieving or transmitting of clinical data”.

- ICH GCP 5.5.3
- 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
- US Guidance for Industry Computerized Systems used in Clinical Investigations. Publ. US Dept Health and Human Services FDA May 2007
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9; 14; Art 26a
- Swiss Federal Act of 19 June 1992 on Data Protection

Before the trial starts, the sponsor is responsible for the development of a number of key documents that include, but are not limited to:

- the protocol and the case report form
- the informed consent and participant’s information sheet (see Module 3.1)

- the investigator's brochure
- the labeling of the IMP
- the master randomization list, if applicable
- decoding procedures in case of blinded trials
- a monitoring plan
- a data management plan and statistical analysis plan

10.5.1.1 Protocol

The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations, and organization of the clinical trial. Details of the IMP are also provided in other documents such as the Investigator's Brochure. The protocol contains a precise trial plan for executing the clinical trial, ensures the safety and well-being of the participants, and provides guidance for the conduct of the trial by several investigators at trial locations. The format and content of the clinical trial protocol has been standardized and is outlined in ICH-GCP Section 6.0.

The protocol must specify:

- the trial administrative information such as trial identification (Eudract number, IND number, protocol number, trial title, phase of drug development), the list of the team members that are responsible for the study (sponsor name, investigators' details, CRO involvement, monitor's name)
- ethical consideration: submission of the protocol to a REC. REC should grant approval on the final version of the protocol.
- that participants or their legal representative(s) must voluntarily confirm their willingness to participate in the trial
- the trial scientific design must stipulate whether it is open-label, randomized, blinded, parallel or cross-over, or factorial design)
- the objectives of the trial (only one primary and a minimum number of secondary objectives. Safety must always be a trial objective)
- how many participants will be recruited and for how long the participants will be included
- in randomized trials, how the treatment will be randomly allocated and by whom (randomization list, central calling center, computerized system)
- who is eligible to participate and who will be excluded (age range, sex, disease status, previous treatment allowed or forbidden, concomitant disease and/or medication, laboratory test values, other tests such as ECG, radiology, scan, etc).
- how the data will be collected (paper case report form or e-case report form), filed, secured, and kept confidential.
- the efficacy and safety assessments and the frequency of tests
- how to report adverse events (AEs) or serious adverse events (SAEs). Any stopping rules in case of excessive toxicity or lack of activity.

- how the IMP or any active drug used as comparator (or placebo, if applicable) will be administered and for how long. When the participants will be taken off the study medication and for which reason(s)
- how to store, handle and maintain accountability of the IMP (or placebo) or any other active product used in the trial
- the responsibility of both the sponsor and the investigator for safety reporting, communication with the REC or regulatory authorities;
- the frequency of monitoring visits and permission to have access to participants' source data for monitors, auditors, and inspectors.
- whether or not an independent Data Monitoring Board will continuously assess safety and/or efficacy data
- how the data will be analyzed, those that will be included or excluded from all or some analyses
- how the data will be published and by whom.

- ICH-GCP 1996 ⇒ Sect. 1.44; 6.0
- EU Directive 2005/28/EC ⇒ Art. 4
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.23
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9, al. 2 lit. a)

10.5.1.2 Case report form

The case report form (CRF), whether it is a printed, optical or an electronic document, is designed to record all of the protocol required information to be reported to the sponsor on each clinical trial participant. The CRF should not include data that are not required by the protocol.

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained for e-data); this applies to both written and electronic changes and corrections (*ICH-GCP 5.18.4 (n)*).

Data recorded in the CRFs must use unambiguous participant identification codes that allow identification of all the data reported for each participant.

When e-CRF or remote electronic data systems are used, the sponsor must ensure that the electronic data processing systems are validated (*ICH-GCP 5.5.3)* and that the systems permit data changes in such a way that changes are documented and that there is no deletion of entered data (maintenance of an audit trail).

10.5.1.3 Investigator's Brochure

An investigator's brochure (IB) is a compilation of the clinical and non-clinical data on the IMP which is relevant to the trial of the IMP in human participants.

The content that should be in the IB is outlined in ICH-GCP section 7.0. The document must be reviewed at least once a year. More frequent updates may be appropriate, depending on the stage of development of the product and the emergence of new information.

There should be sufficient information available from non-clinical or other sources to justify the use of the IMP in a human trial. When new information on the product becomes available, the sponsor should update the IB and make sure that investigators and the REC receive it in a timely manner.

It must be noted that **unexpected serious adverse drug reaction**s (meaning that they are related to the IMP) require an update of the IB and that the sponsor must be promptly distributed the new version to the investigational sites and the RECs.

- ICH-GCP 1996 ⇒ Sect. 1.36; 5.12.1-2; 7.0; 7.5
- EU Directive 2005/28/EC ⇒ Art. 8
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.23(a)(5)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9, al. 2 lit. c)

10.5.2 Data Management

Whatever media is used to manage the data, the confidentiality of the participant must be maintained (*EU 95/46/EC*).

Clinical trial data are transferred from the source documents into the case report forms (CRF). To ensure accurate completion of the CRFs, it is good practice to enter the data into the CRFs as soon as they are available.

During the processing of the trial data, some of them are transformed. It should always be possible to compare the original data with the processed data (*ICH-GCP 5.5.4*). Source data entered directly into CRFs must be defined in a prospective way before the trial starts.

Any electronic filing system or e-records must be used within an adequate document management system that is validated and the access 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 5.5.3)*

Any transfer of ownership of the data should be reported to the appropriate Health Authorities *(ICH-GCP 5.5.10)*

- ICH-GCP 1996 ⇒ Sect. 5.5.3; 5.5.4; 5.5.10
- EU Directive 2001/20/EC ⇒ Preamble (2), (15)
- EU Directive 95/46/EC on Data protection
- 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; 312.62
- 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. 14; 26
- Swiss Federal Act of 19 June 1992 on Data Protection
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 43; 58-60

10.5.3 Investigational Medicinal Product

10.5.3.1 Good Manufacturing Practice (GMP) in Clinical Trials

The sponsor is responsible for ensuring that (*ICH-GCP 5.14.4.*):

- the IMP is at a stage of development that makes it appropriate for use in clinical trials and has been manufactured according to GMP for investigational medicinal products (*ICH-GCP 5.14.5; The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13*).
- the IMP is coded, labeled and packed in a way that protects the blinding whilst allowing it to be rapidly identified in case of emergency
- all parties are aware of how the IMP should be stored and reconstituted, if appropriate
- normally, the IMP formulation **is not changed** during the clinical trial. The formulation may be changed under special circumstances and if it is done, then the data on the changes must be available before the new formulation is used (*ICH-GCP 5.13.1.*)
- the IMP formulation used is stable over the period of its use in a clinical trial. The sponsor should maintain samples of the IMP in case a re-analysis is necessary or required by Health Authorities. The samples should be kept at least until the trial data have been analyzed or else as required by the regulatory authorities, whichever is the longer period.

10.5.3.2 Supply of IMP to Investigational Sites

The sponsor should ensure timely delivery of the IMP to the investigational site. The IMP is distributed to the investigational site only after the REC and the Regulatory Authorities have approved the clinical trial as it is the sponsor's responsibility to have the IMP under control until all approvals are granted (*ICH-GCP 5.14.2; EU 2001/20/EC Art 19 (1 §2), EU The Rules Governing Medicinal Products, Volume 4, Annex 13 §44*).

The sponsor should ensure that written procedures and IMP related-documents are available at the time of IMP shipping to the investigational site. The documents should at least contain instructions for the investigator on the receipt, handling, storage and dispensing of the IMP (*ICH-GCP 5.14.3.*)

10.5.3.3 Availability of IMP for Clinical Trials

Unless under exceptional circumstances set up by the sponsor and approved by Health Authorities, an adequate quantity of IMP shall be made available free of charge by the sponsor

to investigational sites (*ICH-GCP 5.14.1, EU Direct 2001/20/EC Art 19; Swiss comply with ICH*).

In the US, a sponsor must obtain prior written authorization from the FDA to charge for an IMP (*21 CFR 321.8*).

The sponsor must ensure timely delivery of sufficient quantity of the IMP to the investigational site (*ICH-GCP 5.14.4a)*.

- ICH-GCP 1996 ⇒ Sect. 5.13.1; 5.14.1-5
- EU Directive 2001/20/EC ⇒ Art. 19
- 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. 312.8
- Swiss Federal Act of 15 December 2000 on Medicinal Products and Medical Devices ⇒ Art. 6
- Swiss Ordinance of 17 October 2001 on Authorizations in the Field of Medicinal Products ⇒ Annex 1
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

10.5.4 Study Material

The sponsor should provide the investigator with all trial-related material including the protocol, blank case report forms, a sample of the informed consent form and trial information sheet for participants as well as the IB in time for the investigator to review them before agreeing to conduct the trial (*ICH-GCP 5.4.*).

The contract between the sponsor and the investigational site must indicate whether specific material will be needed and will be provided by the sponsor (e.g., ECG machine, laboratory kits, trial-related stickers for sample shipments, etc.).

- ICH-GCP 1996 ⇒ Sect. 5.4
- EU Directive 2001/20/EC ⇒ Art. 1; 2 (e)
- US: no specific references, apply ICH-GCP
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4; 5 lit. b)

10.5.5 Trial Master File (TMF)

Essential documents serve to demonstrate the compliance of both the investigator and the sponsor with the standards of GCP and with all applicable regulatory requirements.

The sponsor is responsible for collecting and maintaining all trial-related essential documents before, during and at the end of the trial (*ICH-GCP 5.5.6*). TMF should be organized as defined in ICH-GCP 8.0, before, during, and at the end of the clinical trial.

The sponsor should ensure, during the entire clinical trial process, that no participant can be identified by their name, including when data are processed by third parties. Privacy and confidentiality rules must be respected (*EU 45/96/EC).*

An electronic filing system or e-records 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. 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 5.5.3*)

- ICH-GCP 1996 ⇒ Sect. 5.5.3; 5.5.6; 8.0
- EU Directive 2001/20/EC ⇒ Art. 15(5)
- EU Directive 2005/28/EC ⇒ Art. 16
- EU The Rules Governing Medicinal Products ⇒ Volume 10, Chapter V: Recommendation on the content of the trial Master File and Archiving
- EU Directive 95/46/EC on Data protection
- 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; 312.62
- US Guidance for Industry Computerized Systems used in Clinical Investigations. Pub US Dept Health and Human Services FDA, May 2007
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 14; Art 26a
- Swiss Federal Act of 19 June 1992 on Data Protection

10.6 Investigator Selection and Agreement

As a sponsor you have an important role to play in the selection of the investigator. You also have to ensure that all agreements are in place before the trial begins.

- **Investigational site**: The sponsor is responsible for selecting the investigator(s)/ institution(s) on the basis of experience, qualifications and availability of adequate resources (*ICH-GCP 5.6.1; 21 CFR 312.53*). If the trial is under US regulation (US-IND, Investigational New Drug), the sponsor must ensure that the investigator is not blacklisted for fraud.
- **Access to participants**: The investigator should be able to demonstrate access to a suitable pool of participants for the trial.
- **Access to staff**: The investigator should have sufficient numbers of qualified staff available for the duration of the trial (*ICH-GCP 5.6.1; 21 CFR 312.53(viii))*

- **Facilities**: The investigator should have adequate facilities (such as laboratories) available for conducting the trial (*ICH-GCP 4.2.1.; 21 CFR 312.53*)

Before entering into an agreement with an investigator/institution, the sponsor should provide the investigator/institution with the protocol and an up-to-date IB and should allow sufficient time for these documents to be studied (*ICH-GCP 5.6.2.*)

The sponsor should obtain the agreement of the investigator/institution to conduct the trial in compliance with GCP and regulatory requirements and with particular conditions specified by the sponsor.

Agreements made by the sponsor with the investigational site and any other parties involved with the clinical trial should be in writing, either as part of the protocol or in a separate agreement. See also ICH-GCP 5.1.4 (*ICH-GCP 5.6.3*).

The monitoring, auditing and inspection of a trial will require access to the source data and document. The sponsor should secure agreement to this from all parties involved, and ensure that the agreement is written into the protocol (*ICH-GCP 5.15.1*).

- ICH-GCP 1996 ⇒ Sect. 5.1.4; 5.6
- EU Directive 2001/20/EC ⇒ Art. 6; 9.1; 9.2
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.50; 312.53
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 8; 9, al. 2 lit. k)
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 10

10.7 Multicenter Trial

A clinical trial conducted according to a single protocol but in more than one site is defined as a multicenter clinical trial (*ICH-GCP 1.40*; *EU 2001/20/EC Art. 2b*).

In multicenter clinical trials, special attention should be paid to issues related to (*ICH-GCP 5.23; 21 CFR 312.53 (iii)*):

- **Compliance**: All participating investigational sites must comply with the protocol and any other regulatory requirements. The sponsor should ensure that they are instructed in how to do this.
- **Additional data**: When investigators are collecting additional data, the sponsor should provide them with CRFs specifically for this purpose.
- **The responsibilities of the coordinating investigator**: The sponsor should document the responsibilities of the coordinating investigator before the trial begins.
- **Communication**: The sponsor must keep each participating investigational site informed of new observations discovered by or reported to the sponsor on the IMP, particularly with respect to safety. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means.

- ICH-GCP 1996 ⇒ Sect. 1.40; 5.6.1; 5.23
- EU Directive 2001/20/EC ⇒ Art. 2 b)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect.312.53; 312.54; 312.55
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 10, al. 3
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 47

10.8 Contract

As a sponsor, you must ensure that a written, dated and signed agreement between you and other involved parties describing any arrangements on delegation and distribution of tasks and obligations (including financial matters) exist before the trial starts and can serve as a basis of a contract (*ICH-GCP 1.17; 5.9*).

All trial-related contracts must be signed before the clinical trial starts.

- ICH-GCP 1996 ⇒ Sect. 1.17; 5.9
- EU Directive 2001/20/EC ⇒ Art. 1.3; 6.3 (j)
- US 21-CFR Parts 54; 312 ⇒ Sect. 54.1-6; 312.52; 312.53
- US FDA form 1572
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ 9, al. 2 lit k); 14, al. 2

10.9 Compensation

No incentives or financial inducements except compensation should be given to trial participants (*EU Directive 2001/20/EC Art. 4)*. While for trial participants receiving compensation, the method and manner of compensation should comply with all applicable regulatory requirements (*ICH-GCP 5.8.3).* Any compensation provided to the trial participant should receive approval from the REC (see also Module 2.1, section 3.8 and Module 3.1, sections 1.4 & 2.4).

10.10 Cost of Treatment for Adverse Events

The sponsor must develop policies and procedures that address the costs of treatment of trial participants in the event of trial-related serious adverse events (e.g., treatments, hospitalization) (*ICH-GCP 5.8.2*).

10.11 Insurance

The sponsor should provide insurance or should indemnify the investigational site against claims arising from the trial, except for claims that arise from malpractice or negligence (*ICH-GCP 5.8.).*

Many countries within the ICH region (but not all) include a basic requirement that no clinical trial may be held without providing insurance or indemnity to cover the liability of the investigator and the sponsor. Where such a requirement exists, each country sets its own standards.

Clinical trials insurance policies have many variables. Some policies are better than others, but an insurance contract should at least provide the following information:

- the country where the insurance policy has been taken (should be taken or should have an office in the country where the trial is performed)
- the period of coverage
- the trial identification (registration number, title, sponsor, development phase)
- the total number of participants in the trial as well as at the precise investigational site
- the minimum limit of compensation per event, per participant, and per trial

- ICH-GCP 1996 ⇒ Sect. 5.8.1
- EU Directive 2001/20/EC ⇒ Art. 3 f); 4 d); 5 d); 6 h), i)
- US: no specific references, apply ICH-GCP
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 7, al. 2; 9, al. 2, lit e)-f)
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 20

10.12 Finances

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigational site (*ICH-GCP 5.9*). The financial aspects of the trial should be part of the documentation submitted to the REC for approval.

In some countries like the USA, investigators are required to sign a "financial disclosure" before the trial starts (*21 CFR 54.1; 21CFR 312.53*); certifying that no financial arrangements between the sponsor and the investigator have been made where the study outcome could affect compensation; that the investigator has no proprietary interest in the tested product; that the investigator does not have a significant equity interest in the sponsor of the study; and the investigator has not received significant payments of other sorts. The sponsor shall obtain a commitment from the investigator to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study. To be note, if a clinical trial is performed under US-IND outside the USA, the investigator must also sign a financial disclosure form.

- ICH-GCP 1996 ⇒ Sect. 5.9
- EU Directive 2001/20/EC ⇒ Art. 9
- US 21-CFR Parts 54; 312 ⇒ Sect. 54.1; 312.53
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 9, al. 2, lit. d)

10.13 Communication with the REC

The sponsor should obtain either from the investigational site or directly from the REC evidence of approval of the clinical trial (*ICH-GCP 5.11.1.*). The approval letter should mention:

- the name and address of the REC
- the list of the REC members who reviewed and granted the approval (*ICH-GCP 8.28*)
- the list of documents reviewed by the REC including version numbers, dates of the documents, language used in the documents *(ICH-GCP 8.27)*
- a clear statement of the REC approval/favorable opinion
- the date when the REC did approve the clinical trial

- ICH-GCP 1996 ⇒ Sect. 5.9; 5.11; 8.27; 8.28
- EU Directive 2001/20/EC ⇒ Art. 9
- US 21-CFR Part 56-Institutional review boards ⇒ Sect. 56.109
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 10; 11
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 45

10.14 Summary of Documents Needed to Start a Clinical Trial

The following list of documents and processes must be in place before the clinical trial can be initiated (the documents may not be limited to the list):

- **Approval**: REC and Health Authorities approval sheets
- **Protocol**: approved by REC and Health Authorities (*ICH-GCP 5.10*)
- **Case Report Form**: paper or electronic version including a guidance document explaining how the CRF must be completed
- **Informed Consent Form**: approved by REC (original version, plus all translated versions). All versions must be approved by REC.
- **Investigator's Brochure**: updated version and approved by REC
- **Randomization list**: if applicable including instructions on how to use it and decoding procedures for blinded trials
- **Contracts**: signed agreements, insurance and financial aspects
- **Curriculum Vitae**: updated version of CV for investigator and sub-investigator(s). Copies of the CVs of the entire team should be on file at the trial site.
- **Signature sheet**: the signature sheet attests the functions, tasks and responsibilities of each team member involved in the clinical trial
- **Laboratories**: normal ranges, accreditation/certification
- **Guidelines**: any trial-specific guidelines (e.g. shipment of samples, communication with central lab, special tests, fluid storage, refrigeration of samples, etc)

- **Plan**: monitoring activities
- **Investigator selection**: site assessment (facilities, laboratory, storage of IMP, source documents, staff availability and training, adequate and sufficient participant availability)

Only once all the documents are available can the sponsor ship the IMP to the investigational site(s).

10.15 Other Documents and Processes

The sponsor should also ensure that the following documents and processes are available prospectively:

- **IDMC** (Independent Data Monitoring Committee): Establishment of an IDMC (role, needs, responsibilities, constitution and membership) to assess the progress of a clinical trial and to make recommendations to the sponsor about its future (*ICH-GCP 5.5.2.*)
- **Safety handling:** establishment of a clear process for ongoing safety assessment of the IMP and notification to regulatory authorities and REC in case of serious adverse drug reactions. Updating all investigational sites on safety new information.
- **Statistical Analysis Plan:** this must be developed before the data are analyzed. The basic analysis plan should be incorporated into the protocol (e.g. sample size calculation, intent-to-treat and per protocol analyses).
- **Electronic data handling**: When handling trial data electronically, the sponsor should use systems that control access to and manipulation of the data in a way that:
    - documents changes made to data and prevents deletion of data
    - maintains the security of the data, especially in the transmission between parties
    - ensures adequate back-up of the data and recovery plans
    - safeguards the integrity of the trial

- ICH-GCP 1996 ⇒ Sect. 5.5.3; 5.5.6-7; 8.0
- EU Directive 2001/20/EC ⇒ Art. 9.2; 9.8
- EU Directive 95/46/EC on data protection
- 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; 312.62
- US Guidance for Industry Computerized Systems used in Clinical Investigations. Publ. US Dept Health and Human Services FDA, May 2007
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 14; Art 26a
- Swiss Federal Act of 19 June 1992 on Data Protection

- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 49

10.16 During the Trial: Documents and Processes

As a sponsor, it is your responsibility to keep a **close watch** on the events during the trial. You have also to ensure that all documents and records are updated and relevant information is made available to all the parties concerned at every stage during the course of the trial.

Therefore, the sponsor or its representative must ensure adequate investigational site monitoring visit activities. Detailed monitoring tasks and responsibilities are described in Section 11 of this module.

10.16.1 REC

When the REC favorably or unfavorably re-evaluates any aspect of a trial, the sponsor should obtain detailed documentation of the change (*ICH-GCP 5.11.3*).

10.16.2 Investigator's Brochure

The Investigator Brochure (IB) should be reviewed at least annually and revised as necessary in compliance with the sponsor's SOPs. More frequent revisions may be appropriate dependent on the generation of relevant new information, such occurrence of unexpected serious adverse reactions for instance (*ICH-GCP 5.12.2; 7.1*).

Special attention should be paid to new unexpected adverse drug reactions originated from ongoing clinical trial activities. The sponsor should promptly inform all investigational sites, update the IB and distribute the new version to all parties.

10.16.3 Protocol and Informed Consent Form

Any revision to the protocol, informed consent form or other information provided to the participants should be documented and implemented during the course of the trial (*ICH-GCP 8.3.2*). New versions of the protocol and informed consent forms should be submitted to the REC, either for approval (major changes) or for information (minor changes) (*ICH-GCP 5.11.2)*.

Some regulatory authorities may require that major changes to the protocol are submitted to health authorities.

10.16.4 Documents issued by the Investigational Sites

During the course of the clinical trial, the sponsor must collect at the investigational site up-to-date documents, such as:

- curriculum vitae of new investigational site staff
- updates to normal values/ranges for medical laboratories or new laboratories procedures

- new lab accreditation or certification
- case report forms and data clarification forms, if any
- updated signature sheet
- IMP accountability (what has been sent, what has been received, what has been used, and what has been returned to the sponsor) (see Section 9.4.4 of this module).

The collection of documents at the investigational site is not necessarily limited to the list above and can be trial-dependent, country-dependent, or sponsor-dependent.

10.16.5 Data Handling

When data are transformed during processing, the originals must not be overwritten (*ICH-GCP 5.5.4.*); an adequate back up and disaster recovery plan must be available.

10.16.6 Managing Safety

The sponsor is responsible for the ongoing safety evaluation of the IMP. The responsibilities, systems and processes of handling safety in clinical trials are detailed in section 12 of this module.

The sponsor must notify the REC, investigators and the regulatory authorities of any findings that could adversely affect the safety of the trial participants; affect the decision to continue the conduct of the trial or alter the REC's opinion (*ICH-GCP 5.16; 5.17.1*).

10.16.7 IMP Supplying and Handling

The sponsor must maintain written records for use of the IMP. The following information should be available in the essential documents

- names and addresses of the investigational sites
- shipment dates, quantity, batch and lot numbers
- conditions of shipment (e.g. maintenance of cool temperature), carrier(s)
- records of batch sample analyses and characteristics

Transfers of IMP from one trial site to another should remain the exception. Such transfers should be defined prospectively and covered by a SOP. The storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability. The product should be returned to the manufacturer for re-labeling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

- ICH-GCP 1996 ⇒ Sect. 5.5.4; 5.14.5; 5.16; 5.17
- EU Directive 2001/20/EC ⇒ Art. 10; 16.4; 17
- EU Directive 2005/28/EC ⇒ Art. 8.3; 9
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 13: Manufacture of investigational medicinal products
- US 21-CFR Parts 312; 511 ⇒ Sect. 312.57; 511.1(b)(3)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 19; 20; 22-25

- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 46

10.17 Premature Discontinuation of the Trial

The decision to prematurely terminate a clinical trial can be taken by the sponsor, the investigator, the REC and even by Health Authorities. In case a trial is prematurely terminated each party has a responsibility to inform the other ones:

- **Sponsor termination**: If the sponsor decides to terminate or suspend a clinical trial, the investigator should inform the investigational site(s), the REC, and the regulatory authorities, if required, and provide a written explanation.
- **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.
- **REC termination**: If the REC terminates or suspends its approval of a trial, the investigator should inform the institution, where applicable, and the sponsor and provide the latter with a written explanation.

Premature discontinuation of clinical trials also requires data analyses and the writing of a final study report (at least in an abbreviated format). The report should be distributed to the investigational sites, the RECS and regulatory authorities, if required.

- ICH-GCP 1996 ⇒ Sect. 4.12; 5.21
- EU Directive 2001/20/EC ⇒ Art. 10 c); 12
- US 21-CFR Parts 312; 314 ⇒ 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); 48

10.18 Sponsor During-Trial Summary

This brings us to the end of the ongoing phase of the Clinical Trial Process

In this section, you have learned that:

- the REC conducts at least one review per year during the course of the trial.
- it is the sponsor's responsibility to:
    - Keep the REC and the investigator informed of all changes that take place during the trial.
    - Ensure the stability of the IMP during the course of the trial.
    - Handle and report safety data
    - Inform the parties in case of premature discontinuation of the trial
    - Keep the trial essential documents up-to-date

10.19 Post-Trial Processes

At trial completion, as a sponsor, it is your responsibility to **ensure** that all documentation and processes are completed as per GCP and regulatory requirements. You need to ensure that the TMF is completed with all essential documents and that reports are written and distributed.

The clinical trial is closed only when all processes are completed and there are no outstanding queries.

10.19.1 At the Sponsor Site

- The sponsor is responsible for the analysis and the writing of the clinical trial report that documents the results and interpretation of the data. The report should be prepared according to regulatory requirements and ICH E3 (*ICH-GCP 5.22.; ICH-Structure and Content of Clinical Study Reports E3, 1995*).
- Any transfer of ownership of the data should be reported to the appropriate authorities as required by the applicable regulatory requirements (*ICH-GCP 5.5.10.*)
- It is good practice and good ethics that clinical trial results are published (WMA, Declaration of Helsinki, 2008, §30).

10.19.2 At the Investigational Sites

- The final close-out of the trial at the investigational site can only be done when the monitor has reviewed all essential documents, all trial data and clarification queries have been collected, the IMP accountability is completed and the trial material returned to the sponsor.

10.19.3 Document Retention and Archives

10.19.3.1 Principles

- Document retention: The sponsor should retain all the trial essential documents as per ICH-GCP 8.0. The period of retention is country-dependent (see also section 10.19.3.2 below and you need to check your local requirements).

  Any transfer of ownership of the data should be reported to the appropriate authorities as required by the applicable regulatory authority requirements (*ICH-GCP 5.5.10*)

10.19.3.2 Records keeping: Variations in Rules and Laws

The Sponsor must archive the clinical trial essential documents as described in ICH-GCP Section 8.0. There is an important variation in Rules and Laws, so the table below provides you with archiving information in each region. You need to check what are your local laws and regulations regarding records keeping and archives.

Topic	ICH	EU	USA	Switzerland
Retention time	at least 2 years after the last approval of a marketing	at least 5 years after completion of the trial or	2 years after a marketing application is	at least 10 years after completion or definitive

Topic	ICH	EU	USA	Switzerland
	application in an ICH region and until there are no pending marketing application in an ICH region. 2 years after formal discontinuation of the IMP clinical development	longer where so required by national regulation	approved for the IMP; or, if an application is not approved for the IMP, until 2 years after shipment and delivery of the IMP is discontinued and FDA has been so notified.	discontinuation of the trial using an IMP. 15 years for medical devices
	ICH-GCP 5.5.11; 5.5.8	EU 2005/28/EC Art. 17 Recommendation on the content of the trial TMF, July 2006	21 CFR 312.57	Swiss Ordinance on Clinical Trials, Art. 25

- ICH-GCP 1996 ⇒ Sect. 5.2.2; 5.5.3; 5.5.8; 5.5.10-12; 5.19.3; 8.0
- EU Directive 2001/20/EC Article 15(5)
- EU Directive 2005/28/EC Article 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 Part 312-Investigational new drug application ⇒ Sect. 312.57; 312.62(b,c)
- US 21-CFR Part 11 ⇒ Sect. 11.10; 11.30, 11.70
- 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

10.19.4 Sponsor Post-trial Summary

This brings us to the end of the final phase of the Clinical Trial Process.

In this section, you have learned that all essential documents are retained by the sponsor as per ICH-GCP 8.0 requirements.

You also learned that it is the sponsor's responsibility to:

- Report transfer of ownership of data to the appropriate authorities, if applicable
- Ensure that the clinical trial reports are prepared and distributed in accordance with the regulatory requirements
- Report safety data to the Health Authorities, the REC and the investigational sites
- Archive all essential documents in a secure place.

11 MONITOR

11.1 Be a Monitor

A clinical trial monitor is appointed by the Sponsor (or its representative) and works under the sponsor's responsibilities. A monitor is an individual who ensure that the conduct of the trial is carried out according to the protocol and all sponsor and regulatory requirements proper at all investigational sites (*ICH-GCP 5.18.2-4*)**.** The monitor must be qualified by training and experience to monitor the progress of the clinical trial (*ICH-GCP 5.18.2; 21 CFR 312.53(d)*)

The purpose of monitoring is to verify that the trial is conducted in compliance with the approved protocol, GCP and health authority's requirements (*ICH-GCP 5.18.1*).

The monitor works in accordance with the sponsor's standard operating procedures (SOPs) and acts as the main line of communication between the investigator and the sponsor (*ICH-GCP 5.18.1*).

11.2 Monitor's Responsibilities

The monitor ensures that:

- the investigational site continues to have adequate resources and facilities to perform the clinical trial
- the investigator has access to sufficient eligible trial participants as planned in the protocol
- all staff members have been trained on the trial and on GCP or retrained
- the investigator provides the required documents at an acceptable quality standard
- the investigational site follows all trial procedures/guidelines, protocol and other trial-related documents
- the IMP is handled, delivered and stored as defined in the protocol
- all participants have signed and dated an informed consent form
- the recruitment complies with the study timelines
- the integrity of clinical trial data is checked against corresponding source documents
- a written report is provided after each on-site visit or communication with the site, stating what was reviewed, deviations or unconformities and the action needed to secure compliance with the trial protocol, GCP, ethics and regulatory requirements

The ultimate responsibility of monitoring and verifying the clinical trial resides with the Sponsor.

11.3 Monitor's Tasks

Regulations do not prescribe a specific monitoring technique, simply stating that the sponsor should determine the extent and nature of monitoring. In general there is a need for on-site monitoring before, during and after the trial (*ICH-GCP 5.18.3; 21 CFR 312.50, 312.56*). The monitor should be familiar with the sponsor's written SOPs, the IMP, the protocol, case report form and any available information needed to carry out the monitoring tasks.

The monitor verifies that the trial adheres to the approved protocol, GCP, and the applicable regulatory requirements (*ICH-GCP 5.18.1*).

11.3.1 Investigational Site Selection

If the monitor is the designated team member to assess the suitability of the investigational site to participate in the clinical trial, the following assessments will include but are not limited to:

- verifying that the investigator has adequate qualifications and time to assume responsibility for conducting a trial (*ICH-GCP 5.18.4 b., 21 CFR 312.53(a))*
- verifying that the investigational site facilities, including laboratories, equipment and staff, are adequate for the safe and proper conduct of the trial and that they will be adequate for the duration of the trial (*ICH-GCP 5.18.4 b.*)
- verifying that the investigator has an adequate number of qualified staff for the duration of the trial
- verifying that the investigator has adequate access to eligible participants by assessing, for instance the history of recruitment in similar trials
- complying with procedures for data recording, reporting and storage
- permitting monitoring, auditing and inspection
- permitting access to source documents

- ICH-GCP 1996 ⇒ Sect. 5.18
- EU Directive 2001/20/EC ⇒ Art. 1.3
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.50; 312.53; 312.56
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ 4; 9, al. 2 lit h)

11.3.2 At the Sponsor Site

11.3.2.1 Before the trial starts

The monitor should receive and review the sponsor's agreed monitoring plan defining the scope of the activities, the frequency of the monitoring visits, and the SOPs to be used to monitor the progress of the clinical trial.

The monitor performs all tasks according to the predefined monitoring plan, before, during and at the end of the clinical trial.

11.3.2.2 During the trial

The monitor acts as the main line of communication between the sponsor and the investigator (*ICH-GCP 5.18.4a*).

The monitor prepares on-site monitoring visits and reviews the previous monitoring reports to identify ongoing issues. New information (safety and/or efficacy) must be forwarded to the investigator

All safety data and queries should be followed up.

An update of the trial status should be written and provided to all investigational sites involved in the study on a regular basis. These documents should be available before the monitoring visit will take place.

Monitoring visit organization: before visiting the investigational site, the monitor will:

- contact the investigator to make a visit appointment
- request that the trial staff be present at the time of monitoring
- request that the case report forms and the source documents be available
- confirm the monitoring visit by phone or by e:mail.

Documents to be available and reviewed before a monitoring visit:

- new information on the safety and/or efficacy of the IMP (if indicated)
- trial status
- previous monitoring report(s)
- protocol and amendment (if any)
- annotated CRF or guideline to complete eCRF
- agenda for the visit
- outstanding CRF queries

Follow-up of on-site visits, the monitor will:

- write a monitoring visit report documenting the activities during the visit and describing the non-compliance and required follow-up actions
- send a thank-you letter to the investigator and document all issues identified during the monitoring visit

11.3.2.3 At the end of the trial

At the end of the clinical trial, all the final documentation, submissions and closures take place in compliance with standards outlined in the monitoring plan.

It is necessary for the monitor to **review** both the investigator (ISF) and sponsor files (TMF) before the trial can be finally closed.

- The monitor should verify reconciliation, return and disposal of the IMP (*ICH-GCP 5.18.4.c.*)
- The monitor should verify that all the investigator's required reports and other written documentation are provided in a timely manner and are of the required standard (*ICH-GCP 5.18.4.l.*)

At the conclusion of the trial, the monitor may be responsible for organizing and archiving all the sponsor-specific essential documents pertaining to the trial. All essential documents contained in the TMF must be filed and archived as per ICH-GCP 8.0. The retention of all essential documents should be done according to local legal and/or regulatory requirements (See section 10.19.3.2 Records keeping).

11.3.3 At the Investigational Site

11.3.3.1 Before the trial starts

Monitoring is the process of tracking a clinical trial to determine its progress, to verify the quality of the data and the adherence to the protocol.

Before the trial starts, the monitor must ensure that all investigational team members have been trained on the trial requirements, that all the material needs to perform the trial are available at the site and that all approvals have been granted.

Once all approvals have been granted, the monitor must ensure that the investigational site receives from the sponsor all the material, documents and information (including the IB) needed to perform the clinical trial (*ICH-GCP 5.18.4*).

11.3.3.2 During the trial

At the site, the monitor must spent enough time to review the CRFs as defined in the monitoring plan to ensure that the data are accurate, legible, and complete against source documents and that the site adheres to the protocol.

The monitor ensures that data entered onto the CRFs correspond to the protocol and the source documents by verifying:

- the informed consent form for all participants (including dates and signatures of both the participant and the investigator) (*ICH-GCP 5.15.2.; 5.18.4e*)
- that all participants met the eligibility criteria
- that the safety parameters are collected, as per protocol; that adverse events and serious adverse events are adequately reported and followed up
- that any withdrawals are documented properly
- that the IMP is safely stored and that the expiry date has not been reached

- that the IMP is administered and accounted for properly and that the dispensing log is maintained correctly.

The monitor also verifies whether the trial staff has changed and obtains, for any new staff, a signed and dated résumé.

At the end of the monitoring visit, the monitor discusses with the investigator any issues identified during the visit. All issues need to be handled by an appropriate corrective action and documented.

- ICH-GCP 1996 ⇒ Sect. 5.15.2; 5.18
- EU Directive 2001/20/EC ⇒ Art. 1.3
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.50; 312.53
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

11.3.3.3 At the end of the trial

The final close-out of a trial can only be done when the monitor has reviewed the investigator files (ISF) and confirmed that all essential documents are appropriately filed.

The trial conclusion should be arranged as for a standard monitoring visit and the following points must be dealt with:

- the review and correction of any outstanding CRFs and queries, including safety issues (e.g. unresolved SAEs)
- collection of all unused, partially used IMP and empty containers. IMP destruction may be take place at the site, if planned and agreed by the PI and the sponsor. The investigator should provide the sponsor with a certificate of destruction.
- collection of all biological samples, if any
- collection of emergency code envelopes, if applicable. Documentation of all code breaks, if any
- ensuring that the site will archive the trial essential documents as required by the institution's archiving procedures and the retention time as per local regulations.
- ensuring that the investigator notifies the REC that the trial is closed, as appropriate
- ensuring that all financial agreements are not pending
- discussing the trial with the investigator to obtain his/her opinion about the trial.

- ICH-GCP 1996 ⇒ Sect. 5.18
- EU Directive 2001/20/EC ⇒ Art. 1.3
- US 21-CFR Part 312-Investigational new drug application ⇒ ⇒ Sect. 312.50; 312.53
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 4

11.4 Monitor Summary

This brings us to the end of the Monitor's roles and responsibilities.

In this section, you have learned that the monitor must:

- be familiar with the information about the IMP as well as with the contents of all the other documentation provided about a trial (protocol, CRF, trial-specific guidelines, contracts, etc.) (*ICH-GCP 5.18.2.*)
- ensure that the investigator receives all the material including the IMP, and documentation necessary and that reports and forms are completed to the standards required (*ICH-GCP 5.18.4.*).
- verify that the investigator conducts the trial in strict compliance with the protocol and any approved amendments and that safety data are timely reported (*ICH-GCP 5.18.4.d.*)
- ensure that the trial staff are performing their specific functions in accordance with the protocol and are not delegating functions to unauthorized people
- communicate deviations to the investigator and take action to prevent their recurrence
- determine that written informed consent was obtained from each participant before the trial began. (*ICH-GCP 5.18.4.e.*)
- review both the investigator and sponsor files and confirm that all necessary documents are appropriately filed in order for the trial to be closed.

12 SAFETY AND PHARMACOVIGILANCE

The sponsor, investigator, independent data monitoring committee (IDMC) and REC have distinct responsibilities with regards to safety monitoring, reporting and trial suspension because of safety concerns. These are discussed in sections 12.3, 12.4 and in module 2.1.

Data and safety monitoring play an essential role in protecting the safety of trial participants and ensuring the integrity of the clinical trial. The objectives of data and continuous safety monitoring are to:

- ensure that risks associated with research participation are minimized to the extent practical and possible
- provide permanent adequate information of the safety (frequency, seriousness, associated factors) to all parties involved in the trial
- avoid exposure of participants to excessive risk
- ensure data integrity
- stop a trial if safety concerns arise or as soon as the trial objectives have been met.

All data and safety monitoring plans must include at a minimum a description of the reporting mechanism of adverse events or serious adverse events to the REC, the sponsor, and appropriate regulatory authorities.

All safety requirements are defined in ICH Guidelines E2a-f. Sponsors must comply with those guidelines. Safety reporting may be country-dependent.

- Current Challenges in Pharmacovigilance: Pragmatic Approaches (Report of CIOMS Working V), Geneva 2001
- EU The rules governing medicinal products ⇒ Volume 9a: Pharmacovigilance
- EU Directive 2001/20/EC ⇒ Preamble (18) ; Art. 10 b)
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.32
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art 22; 23
- Swiss Federal Act of 30 September 2011 related to Research on Human Beings ⇒ Art. 15; 46

12.1 Safety Definition

The following definitions are based on the ICH guidelines for reporting safety data (*ICH-E2 a-f*)

- **Adverse Drug Reaction (ADR)**: In a pre-approval clinical experience with a new IMP or its new usages, particularly as the therapeutic doses may not be established: "all noxious and unintended responses to a medicinal product related to any dose should be considered ADR" *(ICH-GCP 1.1*; *ICH-E2a*).
- **Adverse Event (AE)**: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. So, an AE can be any unfavorable and unintended sign (including abnormal laboratory finding) symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product *(ICH-GCP 1.2*; *ICH-E2a*).
- **Serious Adverse Event (SAE)**: Any untoward medical occurrence that at any dose (a) results in death; (b) is life-threatening; (c) required inpatient hospitalization or prolongation of hospitalization, (d) results in persistent or significant disability/incapacity; (e) is a congenital anomaly or birth defect; (f) is medically significant (*ICH-GCP 1.50; ICH-E2a)*
- **Unexpected Adverse Drug Reaction (UADR)**: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved IMP or the Summary of Product Characteristics for an approved IMP) (*ICH-GCP 1.60; ICH-E2 a*)

CAUSALITY: Causality assessment is required for clinical investigation cases. The causal relationship of the AE to the IMP is usually determined by the investigator. Many terms and scales are in use (*ICH-GCP 4.11; ICH-E2a*). There is no standard international nomenclature, but the most common acceptable terminology today is:

- **Definitely related**: There is a certainty that the event is related to the investigational product.

- **Probably related**: There is high likelihood that the event is related to the investigational product.
- **Possibly related**: There is a likelihood that the investigational product is the cause of the event, but other causes cannot be ruled out.
- **Unlikely to be related**: It is not likely that the event is related to the investigational product, and other more likely causes are present.
- **Unrelated**: Evidence exists that the event is related to something other than the investigational product

- ICH-GCP 1996 ⇒ Sect. 4.11
- ICH-E2A-F
- EU Directive 2001/20/EC ⇒ Art. 2 (m)-(p)
- US: no specific references, apply ICH-E2
- Swiss: no specific references, apply ICH-E2

EXPECTEDNESS: An unexpected ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics, Investigator brochure) should be considered unexpected. When it is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

In a clinical trial, the evaluation of EXPECTED or UNEXPECTED ADR is the responsibility of the sponsor

- ICH-GCP 1996 ⇒ Sect. 5.17
- ICH-E2D 2003
- EU: no specific references, apply ICH-E2
- US: no specific references, apply ICH-E2
- Swiss: no specific references, apply ICH-E2

EXPEDITED REPORTING: Cases of ADR that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected reactions in an expedited manner varies among countries.

In studies conducted under the EU regulatory requirements, serious unexpected ADR and suspected unexpected serious adverse reactions (SUSAR) are to be reported to Regulatory Authorities and the concerned REC within the applicable timeline. The sponsor should ensure that proper processes and procedures are in place to handle this particular safety reporting (in the protocol and at the sponsor site or sponsor representative). This should also take into account the unblinding procedure of the double-blind clinical trials.

Cases of non-serious ADRs, whether expected or not, would not normally be considered reportable on an expedited basis. Non-serious ADRs should be included in the periodic safety update report according to the ICH-E2c guideline

- ICH-GCP 1996 ⇒ Sect. 5.17.3
- ICH-E2C(R1) 1996
- EU Directive 2001/20/EC ⇒ Art. 16-18
- US: no specific references, apply ICH-E2
- Swiss: no specific references, apply ICH-E2

GRADING: The severity of AEs is frequently reported per grades. Generally the protocol defines which grading system will be used in the clinical trial. It can be:

- a 3-level grading system such as:
  - grade 1 = mild
  - grade 2 = moderate
  - grade 3 = severe
- a 5-level grading system such as the Common Terminology Criteria for Adverse Event (CTCAE) that must be used in oncology clinical trials:
  - grade 1 = mild
  - grade 2 = moderate
  - grade 3 = severe
  - grade 4 = life threatening
  - grade 5 = death related to an AE (not disease-related death)

12.2 Manufacturer's Responsibilities

Overall, the drug manufacturer is responsible for producing **QUALITY** IMP as per Good Manufacturing Practice Standards (GMP) for clinical trials (*EU the Rules Governing Medicinal Products Volume 4, Annex 13 on GMP*). GMP requires that the IMP is manufactured, packaged and distributed according to the so-called Annex 13 of GMP quality standards and that IMP is provided to the investigational site free of charge.

In clinical trials, it is the sponsor's responsibility to ensure that GMP processes have been followed and that no defective IMP is sent to the investigational sites. To ensure this, there should be a Qualified Person at the sponsor site who is responsible for the release of the batch number to be used in clinical trials. In case of an adverse event related to the quality of the IMP, it is the sponsor's responsibility to recall all IMP bearing the same batch number.

12.3 Sponsor's Responsibilities

The sponsor must notify the Health Authorities, participating investigators and all RECs of safety concerns associated with the use of an IMP and other trial drug(s)in clinical trials.

The sponsor is responsible for:

- the description of the reporting mechanism of adverse events (AEs) and serious adverse events (SAEs) in the protocol
- processing SAE as reported by the investigators
- identifying whether SAEs are "Suspected Unexpected Serious Adverse Reactions" (SUSAR) to be reported immediately to authorities and quarterly to RECs.
- producing Annual Safety Reports

For all SAEs which qualify for expedited reporting as defined by the sponsor, the sponsor is responsible for informing the Regulatory Authorities, the investigator(s), the monitor(s) and the RECs of the outcome of the medical evaluation. The sponsor must ensure that the Investigator Brochure (IB) is updated within the same time frame as required by the regulatory authorities.

The medical evaluation of the cases is the basis for any recommendation deemed necessary from the sponsor safety department concerning the continuation or discontinuation of a trial.

Safety reports of potential serious risks must be reported:

- within 15 calendar days after the sponsor determines that the information qualifies for expedited reporting;
- no later than 7 calendar days if there has been an unexpected fatal or life-threatening suspected adverse reaction; follow-up reports as applicable must be provided.
- **EXCEPTION**: when death is a study endpoint and the appropriate waiver is obtained. In this case, the report of disease-related deaths is acceptable by the Health Authorities in the annual safety report.

- ICH-GCP 1996 ⇒ Sect. 1.1; 1.2; 1.50; 1.60; 4.11; 5.16; 5.17
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 13: Manufacture of investigational medicinal products
- EU Directive 2001/20/EC ⇒ Preamble (18); Art. 16-18
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.32(c-d)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art. 22-23

12.4 Investigator's Responsibilities

The investigator is responsible for reporting all safety information encountered during the clinical trial. AEs and SAEs are reported in the source documents, the CRF and special reporting forms for SAEs *(ICH-GCP 4.11)*.

All clinical trial AEs are reported at the trial completion in the final study report.

In order to ensure a proper timeframe for reporting SAEs to regulatory authorities and RECs, all SAEs that occur during the course of a clinical trial are reportable immediately (within one working day) to the sponsor, usually via the trial monitor. The investigator should submit all related-SAEs to the REC for information, and to Health Authorities if required.

The monitor must check at each monitoring visit that all identified SAEs were reported to the sponsor within one working day.

- ICH-GCP 1996 ⇒ Sect. 1.1; 1.2; 1.50; 1.60; 4.11; 5.16; 5.17
- EU The Rules Governing Medicinal Products ⇒ Volume 4, Annex 13: Manufacture of investigational medicinal products
- EU Directive 2001/20/EC ⇒ Art 16; 17
- US 21-CFR Part 312-Investigational new drug application ⇒ Sect. 312.32(c-d)
- Swiss Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products ⇒ Art 22-23

12.5 Indepdendent Data Monitoring Committee Responsibilities

The Independent Data Monitoring Committee (IDMC) may be established by the sponsor to assess at regular intervals the safety data and the critical efficacy endpoints. The IDMC may recommend continuing, modifying or stopping the clinical trial.

It is the responsibility of the sponsor to apply the recommendations made by the IDMC.

12.6 REC Responsibilities

The REC should receive any new important safety information that may affect adversely the safety of the trial participants. The continuing review of safety information (i.e. SUSAR, ADR) that are both serious and unexpected may require early termination of the trial.

In case of safety concerns, REC may suspend or remove its approval.

12.7 Use of Dictionary

For analysis purpose, AE and SAE need to be standardized to provide a comprehensible clinical report. The use of the MedDRA (Dictionary for Regulatory Activities) is mandatory for all trials that support a registration dossier.

In brief, MedDRA is NOT a dictionary defining terms, but

- MedDRA terminology standardizes AE original terms prior to analysis of clinical trial results
- MedDRA terminology applies to all phases of drug development including post-registration studies, but excluding data from animal studies.
- MedDRA consists of 26 System Organ Classes (SOC) listing more than 60,000 terms. There are 5 hierarchical levels of coding from the lowest level term (LLT) up to the high level term (SOC)

Investigators should pay attention to the terminology used to complete the CRFs in order to avoid misinterpretation of the study results (especially in some Phase I trials where the Maximum Tolerated Dose is based on the Dose Limiting Toxicity). For instance MedDRA does not treat the following information in the same way:

- decrease in white blood cell count is classified as “Investigation SOC”
- neutropenia is classified as “Blood disorders”

If the investigator uses an inappropriate terminology, the toxicity profile of the IMP may be diluted, inaccurate or misleading.

Investigators should ensure that all lab abnormalities are accurately reported in the AE section of the CRF

12.8 International collaboration

The principle of international collaboration in the field of pharmacovigilance is the principal basis for the WHO International Drug Monitoring Program through which over 80 member nations have systems in place to record and report adverse effects of drugs in their patients.

12.9 Pharmacovigilance in Europe

The pharmacovigilance effort in Europe is coordinated by the European Medicines Agency (EMA) and conducted by the national competent authorities (see EU Volume 9a). The main responsibility of the EMA is to maintain and develop the pharmacovigilance database consisting of all suspected serious adverse reactions to medicines observed in the EU. The system is called EudraVigilance.

12.10 Pharmacovigilance in the United States

Three primary branches of pharmacovigilance in the U.S. include the FDA, the pharmaceutical manufacturers, and the academic/non-profit organizations (such as RADAR Research on Adverse Drug Event and Reports). **MedWatch** is also a FDA reporting system for AEs and SAEs. The MedWatch system collects reports of adverse reactions and quality problems, primarily with drugs and medical devices, but also for other FDA-regulated products.

13 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
EMA	European Medicine Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registrations of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
REC	Institutional Review Board (IRB) or Independent Ethics Committee (IEC)
ISF	Investigator Site File

MD	Medical Doctor (Physician)
MedDRA	Dictionary for Regulatory Activities
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

14 GLOSSARY

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment (to the protocol)

See Protocol Amendment.

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail

Documentation that allows reconstruction of the course of events.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study (ICH)

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial (EU)

'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

Clinical Trial/Study Report (ICH)

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Clinical Trial

Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicentre trial.

Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Electronic Record (US 21CFR Part 11.2)

Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved or distributed by a computer system.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product (ICH)

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigational Medicinal Product (EU)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled

(formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

Multicenter Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical Study

Biomedical studies not performed on human subjects.

Non-interventional trial

a study 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

Opinion (in relation to Independent Ethics Committee)

The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record

See Source Documents.

Protocol (ICH)

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol (EU)

A document that describes the objective(s), design, methodology, statistical considerations and organization of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator (ICH 1.54, FDA 21-CFR 312.3)

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sub-investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site

The location(s) where trial-related activities are actually conducted.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other

vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

15 REFERENCES

World Medical Association: Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants 59th WMA General Assembly, Seoul, Korea, October 2008; [HL: **http://www.wma.net/en/30publications/10policies/b3/|**

World Health Organization: Good Clinical Laboratory Practice**.** Special Program for Research and Training in Tropical Disease (TDR), 2009
http://www.who.int/tdr/publications/documents/gclp-web.pdf

International Conference on Harmonisation (ICH)
[HL: http://www.ich.org/products/guidelines.html]

- **ICH E1-E2F**: Clinical safety
- **ICH E3**: Clinical study reports
- **ICH E4**: Dose response studies
- **ICH E5**: Ethnic factors
- **ICH E6**: Good clinical practice
- **ICH E7**: Special populations: Geriatrics
- **ICH E8**: General considerations for clinical trials
- **ICH E9**: Statistical principles for clinical trials
- **ICH E10**: Choice of control group and related issues in clinical trials
- **ICH E11**: Clinical investigation of medicinal products in the pediatric population
- **ICH E12**: Principles for clinical evaluation of new antihypertensive drugs
- **ICH E13**: none
- **ICH E14**: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
- **ICH E15**: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics: Genomic data and sample coding categories
- **ICH E16**: Biomarkers related to drug or biotechnology product development: context, structure and format of qualification submissions

- **ICH S1A-S1C**: carcinogenicity studies
- **ICH S2**: genotoxicity studies
- **ICH S3A-S3B**: toxicokinetics and pharmacokinetics
- **ICH S4**: toxicity testing
- **ICH S5:** reproductive toxicology
- **ICH S6**: biotechnological products
- **ICH S7A-S7A**: pharmacology studies
- **ICH S8**: immunotoxicology studies
- **ICH S9**: nonclinical evaluation for anticancer pharmaceuticals
- **ICH S10**: photosafety evaluation

European Union "The rules governing medicinal products in the European Union": Volume 10 - Clinical Trials Regulations
[HL: http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm]
Volume 10 contains guidance documents applying to clinical trials.

Chapter II: Monitoring and Pharmacovigilance

- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (June 2011)
- ICH guideline E2F - Note for guidance on development safety update reports (September 2010)

Chapter IV: Inspections

- Guidance for the preparation of GCP inspections (June 2008)
- Recommendation on inspection procedures for the verification of good clinical practice compliance (July 2006)
- Guidance for the conduct of GCP inspections (June 2008)

Chapter V: Additional Information

- Guidelines on good clinical practice (ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95) (1996)
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (December 2009)
- Recommendation on the content of the trial master file and archiving (July 2006)

Chapter VI: Legislation

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).

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- **Annex 13:** Manufacture of Investigational Medicinal Product
- **Annex 16:** Certification by a Qualified Person (QP) and batch release

Swiss Laws and Ordinances.

- Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA
- Ordinance of 17 October 2001 on Clinical Trials of Therapeutic Products (OClin)
- Ordinance of 17 October 2001 on the authorizations in the field of medicines
- Federal Act of 30 September 2011 related to Research on Human Beings (not yet in force)

USA Food and Drug Administration (FDA): Code Title 21 Code for Federal Regulations - Food and Drugs (21-CFR) (updated every year in April)
[HL: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?sid=b33d9356b74127377605eadc7f0aec46&c=ecfr&tpl=/ecfrbrowse/Title21/21cfrv1_02.tpl]

- Part 11: Electronic records, electronic signatures
- Part 50: Protection of human participants
- Part 54: Financial disclosure by clinical investigators
- Part 56: Institutional Review Boards
- Part 312: Investigational new drug application
- Part 314: Application for FDA approval to market a new drug
- Part 511: New animal drugs for investigational use