Conducting a clinical trial is a complex procedure, generally lasting one or more years, usually involving numerous participants and several trial sites. It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing clear and transparent procedures and creating conditions conducive to the effective coordination of such clinical trials by the authorities concerned.

The accepted basis for the conduct of the clinical trials in the humans is founded in the protection of the human rights and the dignity of the human being with regard to the application of the biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through the risk assessment based on the results of the toxicological experiments prior to any clinical trial, rules on the protection of the personal data, screening by the ethics committee, and competent authorities.

Before commencing any clinical trial, the sponsor shall be required to submit a valid request for the authorisation to the ethics committee, and competent authority in which the sponsor plans to conduct the clinical trial.

All clinical trials, including the bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of the good clinical practice. The good clinical practice is a set of the internationally recognised ethical and scientific quality requirements which must be observed for the designing, conducting, recording and reporting the clinical trials that involve the participation of the human subjects. The compliance with this good clinical practice provides assurance that the rights, safety and well-being of the trial subjects are protected, and that the results of the clinical trials are credible.

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WALADKHANI CONDUCTING CLINICAL TRIALS

Dr. Ali-Reza Waladkhani, PhD

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A theoretical and practical guide

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DR. ALI-REZA WALADKHANI, PHD

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Dr. Ali-Reza Waladkhani, PhD

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AE	Adverse event
CDRH	Centre for Devices and Radiological Health
CEN	European Committee for Normalization
CHMP	Committee for the Medicinal Products for Human Use
COMP	Committee on the Orphan Medicinal Products
CRA	Clinical research associate
CRF	Case report form
CRO	Clinical research organisation
CT	Clinical trial
CVMP	Committee for the Medicinal Products for Veterinary Use
DFS	Disease free survival
DQF	Data Query Form
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EC	Ethic committee
EMEA	European Agency for the Evaluation of the Medicinal Products
ESF	European Science Foundation
EU	European union
FDA	Food and drug administration
GCP	Good clinical practice
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
HMPC	Committee on the Herbal Medicinal Products
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Independent review board
IsoP	International Society of PharmacoVigilance
ITT	Intention to treat
LOCF	Last-Observation-Carried-Forward
MABEL	Minimal Anticipated Biological Effect Level
MAUDE	Manufacturer and User Facility Device Experience Database
MAUDE	Manufacturer and User Facility Device Experience Database
MSCA	Member State Competent Authorities
NDA	New drug application
NIH	The American National Institutes of Health
NOAEL	No Observed Adverse Effect Level
PFS	Progression free survival
PSUR	Periodic Safety Update Report
SAE	Serious adverse event
SOP	Standard operating procedure
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
WHO	World health organisation
WMA	World Medical Association

1. Introduction

Medicine is extremely conservative in nature, and it takes many years for a treatment to become generally available even after it has shown promising results in the patients. The accepted basis is the conduction of the clinical trials in the humans. For the first time the clinical trials were introduced in the 1020 AC. Avicenna[1] in his book "The Canon of Medicine[2]" has laid down rules for the experimental use of the drugs. He has written a precise guide for practical experimentation, which form the basis for the modern clinical trials. Following rules and principles have been laid down for testing the effectiveness of the new drugs and medications:

- "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."
- "The drug must be free from any extraneous accidental quality."
- "The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones."
- "It must be used on a simple, not a composite, disease."
- "The quality of the drug must correspond to the strength of the disease."
- "The time of action must be observed, so that essence and accident are not confused."
- "The effect of the drug must be seen to occur constantly or in many cases."

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[1] Abu Ali al-Husayn ibn Abd Allah **ibn Sina** was a Persian philosopher, polymath, and the foremost physician of his time. Ibn Sina wrote almost 450 treatises on a wide range of subjects. In particular, 150 of his treatises concentrate on philosophy and 40 of them medicine.

[2] The Canon of Medicine is a 14-volume Arabic medical encyclopedia, which was completed in 1025 AC. This Arabic book was based on a combination of Avicenna own personal experience, and medieval Islamic medicine. It is considered as one of the most famous books in the history of medicine.

The clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites. It is any investigation in the human subjects intended to discover or verify:

- the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal product(s), or
- to identify any adverse reactions to one or more investigational medicinal product(s), or
- to study the absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety or efficacy.

It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing clear and transparent procedures and creating conditions conducive to the effective coordination of such clinical trials by the authorities concerned.

For the medicinal products procedures for the authorisation and supervision of the medicinal products for the human and veterinary use, which include the products with intention for the gene therapy or cell therapy, prior scientific evaluation is mandatory before the competent authority grants the marketing authorisation. In the course of this evaluation, full details of the results of the clinical trials on which the application for the marketing authorisation is based and, consequently, on the manner in which these trials were conducted and the same committee may go so far as to require the applicant for such authorisation to conduct further clinical trials.

The accepted basis for the conduct of the clinical trials in the humans is founded in the protection of the human rights and the dignity of the human

being with regard to the application of the biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through the risk assessment based on the results of the toxicological experiments prior to any clinical trial, rules on the protection of the personal data, screening by the ethics committee, and competent authorities. All clinical trials, including the bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of the good clinical practice. The good clinical practice is a set of the internationally recognised ethical and scientific quality requirements which must be observed for the designing, conducting, recording and reporting the clinical trials that involve the participation of the human subjects. The compliance with this good clinical practice provides assurance that the rights, safety and well-being of the trial subjects are protected, and that the results of the clinical trials are credible. The principles of the good clinical practice and detailed guidelines in line with those principles shall be adopted and, if necessary, revised to take account of the technical and scientific progress.

Before commencing any clinical trial, the sponsor shall be required to submit a valid request for the authorisation to the competent authority in which the sponsor plans to conduct the clinical trial. Also, the written authorisation may be required before the commencement of the clinical trials for such trials on the medicinal products which do not have a marketing authorisation, and other medicinal products with the special characteristics, such as the medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of the human or animal origin, or contains the biological components of the human or animal origin, or the

manufacturing of which requires such components. The following points must be considered before starting the clinical trials:

- The foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients,
- The positive vote in favour by the ethics committee,
- The competent authority has not objected within a given period,
- Continuing only if the compliance with the applicable requirements is permanently monitored,
- The well informed trial subject or his legal representative,
- The trial subject has given his/her written consent after understanding the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted,
- The rights of the subject to the physical and mental integrity, to privacy and to the protection of the data concerning him, and
- The provision has been made for the insurance or indemnity to cover the liability of the investigator and sponsor.

2. Preclinical Studies

Before any new drug can be given to the humans, it must go through the extensive pre-clinical testing in the animals. The likely nature of the side effects and the required effective dose can be extrapolated from the animal results, but there can still be surprising since the animals are quite different from the human. These studies must adhere to the GLP[3] in ICH[4] Guidelines to be acceptable for the submission to the regulatory agencies

Appearance and disappearance of the drug concentrations in whole blood or blood components are the primary measures of the drug movement into the target tissues. The pharmacologic effects occur when the drug reaches these sites in the appropriate amounts. The non-clinical studies will be carried out in the animals (in-vivo) and in-vitro. These studies include:

- The pharmacology,
- The pharmacokinetic, and
- The toxicology.

The special attentions of the pharmacological and toxicological tests are:

- To show the adequately investigation of the proposed therapeutic use,
- To investigate the potential undesirable pharmacodynamic effects of the substance on the physiological functions, which will be performed at exposures in the anticipated therapeutic range and above,
- To show the potential toxicity of the product and any dangerous or undesirable toxic effects,

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[3] The GLP (Good Laboratory Practice) refers to a system of the management controls for the laboratories, and research organisations to ensure the consistency and reliability of the results.

[4] The ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) is a project to bring the regulatory authorities and experts from the pharmaceutical industries together. The regions of interests are to discuss scientific and technical aspects of the pharmaceutical product registration.

- To show the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in the human beings, and
- To collect the data about the therapeutic and toxicological potential of the product.

2.1. Pharmacokinetic

The pharmacokinetic is a science that deals with the progressive movement and alteration of the chemical substances within the body. The pharmacokinetic is the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances. The pharmacokinetic investigation of all pharmacologically active substances will allow comparison and extrapolation between the animal and human. Also, the pharmacokinetic shows:

- The absorption,
- The distribution,
- The metabolism, and
- The elimination of substances in an organism.

The pharmacokinetic studies will be carried out mainly by means of the physical, chemical or possibly by biological methods, and by the observation of the actual pharmacodynamic activity of the substance itself. The information on the distribution and elimination will be collected in all cases where such data are indispensable to determine the dosage for the humans, and in respect of the chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

The bioavailability is important when reviewing the effects or pharmacology of a drug. In order for a drug to have an effect, it needs to be physically present at the site where it exerts its pharmacological action. First the drug needs to be absorbed, and then it needs to be distributed or transported to a receptor[5]. The drug may then exert its pharmacological effect. Subsequently, the drug may be metabolized and then excreted.

In order to understand the drug dosing, one needs to appreciate how the amount of the drug in the bloodstream changes after the administration of the drug. The pharmacologists will frequently employ a graph of the serum concentrations of a drug vs. time in order to describe the drug's bioavailability. The relative amount of the absorbed drug compared with the administered drug is referred to as the drug's bioavailability. The total bioavailability and the time course of absorption affect the drug action. Even while the drug is being absorbed, the processes of the distribution, metabolism, and elimination are already at work affecting the serum levels. When a drug leaves the bloodstreams and accumulates in another tissue, this lowers the serum level. Sometimes, this will increase the activity of the drug, particularly for the drugs that exert their effects in the tissues other than the bloodstream. The general anaesthetics and antidepressants have their effects in the CNS. Other drugs may accumulate in the adipose tissue, only to be released slowly over an extended period of time. The extent of the drug absorption is integral in determining the duration, termination, intensity, and

[5] The receptor is a protein on the cell surface (membrane) or within the cells that binds to a specific molecule e.g. neurotransmitter, hormones, and drugs. This binding will initiate the cellular response to the bonded proteins. This may induce changes in the behaviour of the receptor proteins, which may result in the physiological changes that constitute the biological actions of the bonded proteins. The cells can increase (upregulation) or decrease (downregulation) the number of the receptors to a given hormone, neurotransmitter, or drug to alter its sensitivity to this molecule.

therapeutic index of the drug. For most drugs, the rate of the absorption can be classified as:

- A zero-order rate process. The zero-order rate process proceeds in a constant fashion and without regard to any other factors. In terms of the drug absorption, a certain amount of the drug will be absorbed in a given time period and will not change. Usually, the zero-order absorption is the result of the specific drug carriers working at their maximal capacity.
- A first-order rate process. The first-order rate process differs considerably from that of a zero-order process. The first-order rate process will increase as the concentration of the drug at the absorption site increases. In terms of the drug absorption, the rate of the drug absorption increases as the drug concentration at the absorption site increases.

2.1.1. Absorption

Absorption is the movement of a drug into the bloodstream. It involves several phases. First, the drug needs to be administered via route of the administration (e.g. oral, dermal, etc.), and in a specific dosage form (e.g. tablets, infusion, etc.). Many factors affect the absorption:

- The route of the administration,
- The chemical nature of the drug, and
- The local environment at the site of the absorption e.g.
  - The pH,
  - The blood flow, and
  - Physiological changes of the tissue.

Further, the absorption may be influenced by the gastrointestinal tract motility, the prior surgery to the gastrointestinal tract, simultaneous intake of the food, and many other factors. The weakly acidic drugs are generally

absorbed in the stomach, while weakly basic drugs are absorbed in the small intestine. Most drugs are weakly basic.

The overall rate of the drug absorption represents the sum of many individual rates of the processes that eventually lead to the appearance of the drug in the bloodstream. These individual rates include:

- The rate of the disintegration of the dosage form,
- The rate of the dissolution of the drug from the disintegrated dosage form,
- The rate of the gastric emptying,
- The rate of the drug degradation in the gastrointestinal tract, and
- The rate of the intestinal emptying.

2.1.2. Drug dissolution

The dissolution rate of many drugs is slower than the overall rate of the drug absorption. For such drugs, the dissolution rate limits their absorption. The tablets, capsules, and other compressed, oral dosage form typically belong to this category. The circumstances that influence the dissolution rate for these drugs will have a substantial impact on the drug absorption. The weakly basic drugs dissolve well in the acidic environments and the weakly acidic drugs dissolve well in the basic environments.

2.1.3. Distribution

The distribution of a drug between the different tissues is dependent on the permeability[6] between the tissues, blood flow, perfusion[7] rate of the tissue, and the ability of the drug to bind the plasma proteins, and tissue. The drugs can

[6] The permeability is the movement of the fluids and molecules between the different body tissues in particular between the blood and tissues.
[7] The perfusion is the process of the nutritive delivery of the blood to a tissue.

be water soluble or un-soluble. Also, depending on the drugs chemical nature, the drug may preferentially concentrate in a particular tissue.

- The water-soluble drugs: remain in the fluid compartment, and
- The water-un/soluble drugs: preferentially accumulate in the adipose tissue.

2.1.4. Metabolism

In the body drugs will encounter the metabolic processes that may alter its chemistry. The metabolic processes in the body tend to decrease the toxicity and enhance the elimination of the foreign chemicals. These paired processes occur by the three principal mechanisms:

- Increasing the water solubility of these chemicals,
- Decreasing the size of the foreign molecules, and
- Binding of the drugs to the larger molecules (conjugation).

The end products of these processes are referred to as the metabolites. The metabolism can occur in the peripheral tissue of the body or in a specific organ. The liver is frequently the organ involved in this process. Many enzymes[8] participate in the drug metabolism. One group of the liver enzymes responsible for much of this activity is the cytochrome P450 enzymes. The changes in the liver function may also affect the drug metabolism. In the absence of the liver pathology age alone will affect the drug metabolism.

[8] The enzymes are proteins that accelerate the chemical reactions. In these reactions, the molecules will be converted into the different molecules, the products. Almost all processes in the cell need the enzymes in order to occur at the significant rates. The enzymes are extremely selective for their substrates, and speed up only a few reactions from among many possibilities. The set of the enzymes made in a cell determines which metabolic pathway will occur in that cell.

2.1.5. Elimination

Several organs are involved in eliminating the drugs from the body. The kidneys are the most important organs in this regard. These organs of the homeostasis remove the drugs and drug by-products from the circulation by both the passive action (filtration) and by the active processes involving the secretion, and the resorption of the substances from the plasma. The substances processed by the kidney may be actively or passively secreted into the urine as it traverses the nephron[9], which is the functional unit of the kidney. The substances can also be actively or passively reabsorbed into the bloodstream before leaving the nephron. This process can be affected by the pH of the urine and can be enhanced or inhibited by the presence of other substances in the urine or the blood. The lungs, the liver, the skin, and various glands may also help in the elimination of the chemicals from the body. Age is a factor in the declining the renal function and thus hinders the drug elimination.

2.1.6. Nutritional Status

The presence of the nutritional abnormalities may have an effect on the drugs. The drug dosages may need adjustment based on the actual body weight for some drugs. Other drugs may need to be dosed differently in the obese, normal, and underweight patients, based on the actual, ideal, or on adjusted body weight corrected for the lean body mass. The somatic protein status may affect the dosing of the medications that bind to the somatic protein.

[9] The nephrons regulate the water and soluble substances by filtering the blood, reabsorbing some substances, and excreting the rest as the urine. The nephrons eliminate the wastes from the body, regulate the blood volume, and pressure, control the levels of the electrolytes, and regulate the blood pH.

2.2. Pharmacodynamic

The pharmacodynamic studies should address the mode of the action, and provide the knowledge on the biology of the target. Also, it is the study of the drug actions. It should include:

- The receptor binding and occupancy,
- The duration of the effect, and
- The dose-response.

The fewer systems affected by the drug, the more specific its action. Specifically acting the drugs are generally considered better to work with from a pharmacodynamic perspective. The drugs that interfere directly with another drug's action would cause a drug-drug interaction. The drugs with an effect similar to another drug may cause a greater than the additive pharmacological effect. This type of the interaction is called synergism. The drugs with the opposing pharmacological effects may negate the benefits of one of the agents. The drugs can be categorized as exerting an action:

- In a general manner affecting all body tissues, and cells, and
- In a specific manner having a target substrate that they act on, in one or more organ systems.

2.2.1. Toxicology

The toxicology is the study of the adverse effects of the drugs on the living organisms e.g. symptoms, mechanisms, treatments, and detection of poisoning. The chief criterion regarding the toxicity of a chemical is the dose, i.e. the amount of the exposure to the substance. As Paracelsus[10] said "All

[10] Paracelsus was born in December 1493 in Switzerland. He is the father of the modern toxicology.

things are poison and nothing is without poison, only the dose permits something not to be poisonous". The toxicological studies could occur as:

- A single-dose toxicity test which means a qualitative and quantitative study of the toxic reactions, which result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physicochemical state in which they are present in the actual product, and
- The repeated dose toxicity tests, which are intended to reveal any physiological and/or anatomic pathological changes induced by the repeated administration of the active substance or the combination of the active substances under the examination. The repeat-dose toxicity allows the determination of how these changes are related to the dosage. It will be performed as:
  - The short term, which last two to four weeks, and
  - The long term, which last depend on the conditions of the clinical use. It describes the potential adverse effects.

2.2.2. Geno-toxicity

The purposes of the study of the mutagenic[11] and clastogenic[12] potential is to reveal the changes which a substance may cause in the genetic material of the individuals or cells. The mutagenic substances may present a hazard to the health since the exposure to a mutagen carries the risk of inducing the germ-line mutation,

- With the possibility of the inherited disorders, and

[11] The substances with the mutagenic potentials will change the genetic information (usually DNA) of an organism. This cause increases the number of the mutations above the natural background level.
[12] The substances with the clastogenic potentials will cause the damages to the chromosomes, such as breaks in or change in the amount of the proteins.

- The risk of the somatic mutations including those leading to the cancer.

2.2.3. Carcino-genicity

The tests to reveal the carcinogenic[13] effects will be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner. Further, the carcino-genicity tests will be performed for some medicinal products if there is concern about their carcinogenic potential, e.g. from the product of the same class or the similar structure, or from evidence in the repeated dose toxicity studies.

2.2.4. Repeated Dose Tissue Distribution

The repeated dose tissue distribution studies are an important component in the non-clinical studies. The single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of the tissue distribution and the potential for the accumulation. These studies have only to be conducted when the appropriate data cannot be derived from other sources. The tissue distribution studies are essential in providing the information on the distribution and accumulation of the compound and/or metabolites, especially in relation to the potential sites of the action. One week of the dosing is normally considered to be a minimum period. A longer duration should be selected when the blood/plasma concentration of the compound and/or its metabolites does not reach the steady state. It is normally considered unnecessary to dose for longer than three weeks.

[13] The carcinogen is any substances, or agents which cause cancer.

2.2.5. Reproductive and Developmental Toxicity

Investigation of possible impairment of the male or female reproductive function as well as the harmful effects on the progeny will be performed by the appropriate tests. These tests comprise the studies of the effect on the adult male or female reproductive function. When the medicinal product is administered to a female during the pregnancy studies of the toxic and teratogenic[14] effects at all stages of the development from the conception to the sexual maturity, as well as the latent effects will be performed. Further, additional studies will be performed addressing the development when administering the medicinal product of the offspring.

The embryo/foetal toxicity studies will normally be conducted on the two mammalian species, one of which should be a non-rodent mammal. The prenatal and postnatal studies shall be conducted in at least one species. In the case of the similar metabolism of a medicinal product in a particular species the tests have to include this species.

2.2.6. Local Tolerance

The local tolerance studies will indicate whether the medicinal products are tolerated at the sites in the body, which may come into the contact with the medicinal product as a result of its administration in the clinical use. The local tolerance testing will be conducted with the preparation being developed for the human use, using the vehicle and/or excipients in treating the control group(s). The design of the local tolerance tests (choice of species, duration, frequency, and route of administration, and doses) is dependent on what is to

[14] The teratogenic studies investigate the frequency, causation, and development of the congenital malformations.

be investigated and the proposed conditions of the administration in the clinical use.

For the chemicals applied to the skin (e.g. dermal, rectal, and vaginal) the sensitising potential has to be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

2.2.7. Environmental Risk Assessment

A risk assessment overview must evaluate the possible risks to the environment due to the use and/or disposal of the medicinal product. It must make proposals for the appropriate labelling provisions about the environmental risks connected with the release of the Genetically Modified Organisms containing or consisting in the medicinal products.

2.2.8. Safety Pharmacology

The safety pharmacology studies are defined as those studies which investigate the potential undesirable pharmacodynamic effects of a substance on the functions in relation to the exposure in the therapeutic range and above. In particular, for the medicinal products targeting the immune system, the potential unintended effects should be investigated, e.g. using the in-vitro studies, including the human material. The Animal models that are thought to be similar to the human disease may provide further insight in the pharmacological action, the pharmacokinetics, and dosing in the patients. They may also help the determination of the safety. The following factors have to be considered e.g.

- The results from the previous safety pharmacology studies.
- The effects related to the therapeutic effects of the test substance.

- The Adverse effects associated with the members of the chemical or therapeutic effect.
- The ligand binding or enzyme assay data suggesting a potential for the adverse effects.

The safety pharmacology studies have to be designed for defining the dose-response relationship of the adverse effect observed. The time course (e.g., onset and duration of response) of the adverse effect has to be investigated. Generally, the doses eliciting the adverse effect have to be compared to the doses eliciting the primary pharmacodynamic effect in the test species or the proposed therapeutic effect in the humans.

2.2.9. Calculation of First Dose in Man

The calculation of the first dose of the investigational products in man is based on the "No Observed Adverse Effect Level" (NOAEL) determined in the non-clinical safety studies performed in the most sensitive and relevant animal species, adjusted with the allometric[15] factors or on the basis of the pharmacokinetics. After the first calculation this dose will be reduced or adjusted by the appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials. Another method of the calculation is the use of the 'Minimal Anticipated Biological Effect Level' (MABEL[16]). This method should be used for the calculation of the first dose of the high-risk investigational products. In order to further limit the potential for the adverse reactions in the humans, the safety factors should take into account the criteria of the risks such as

[15] The allometry is the science of studying the differential growth rates of the parts of a living organism's body part or process. Also, it refers to change in proportion of the body size (mass and volume) relative to the body area.

[16] MABEL is the anticipated dose level leading to a minimal biological effect level in humans.

- The novelty of the active substance,
- The biological potency and its mode of action,
- The degree of the species specificity, and
- The shape of the dose-response curve.

3. Clinical Trials

The clinical trials can be divided into the observational and interventional studies. During the observational studies the research subjects will be observed and their outcomes will be assessed by the investigators. Also the investigators do not actively manage the trials. In contrast to the observational studies during the interventional studies the research subjects will be given a particular medicine or intervention. Also the investigators will actively assess how the health of the research subjects changes. The clinical trials can also be divided into five different types:

1. The clinical trials for the treatment of the disease.
2. The clinical trials for the disease prevention.
3. The clinical trials for the new diagnostic procedures.
4. The clinical trials for determining the best way to assess the subject health and disease condition.
5. The clinical trials for assessing the subject quality of life

The clinical trials to evaluate the new drugs, medical devices, biologics, or other interventions on the research subjects have to be performed in strictly scientifically controlled settings, and are required for the regulatory authority approval. They are designed to assess:

- The safety and efficacy of an experimental therapy,
- To assess whether the new intervention is better than the standard therapy, or
- To compare the efficacy of two standards or marketed interventions.

A comparative trial of the treatments typically comprises several sequential phases:

- The determination of a subject's eligibility for the study,

- The research subject's entry into the study,
- The assignment of the treatments,
- The care itself,
- The evaluation of the subject's outcome,
- The statistical analysis of the data, and
- The reporting.

The clinical trials are commonly classified into four phases and the drug-development process will normally proceed through all four stages over a period of many years. If the drug successfully passes through the first three phases, it is usually successfully approved for the use in the general population.

3.1. Phase-I Clinical Trials

The Phase-I clinical trials are dose finding studies where the primary objective is to determine the maximum tolerated dose of the treatment and to define the toxicities of the treatment. Normally a small (20-80) group of the healthy volunteers (with the exception of the drugs for the treatment of the HIV, Cancer, Parkinson, Alzheimer disease, and coronary heart disease), or the patients (only the drugs for the treatment of the HIV, Cancer, Parkinson, Alzheimer disease, and Coronary heart disease) will be selected. A Phase-I clinical trial can be theoretically divided in the Phase-Ia and Phase-Ib. The Phase-Ia represents the first test of the treatment in the people. The classic Phase-Ia clinical trial is only intended to determine the dose and characterize the side effects. Attention should also be given to:

- The calculation of the initial dose, which will be used in the humans for the first time,
- The subsequent dose escalations,

- The intervals between doses to the different individuals, and
- The management of the adverse effects.

For the high-risk medicinal products which are defined as potential when there are concerns that the serious adverse reactions in the first-in-man clinical trials may occur their development program requires the special consideration. Normally a Phase-I clinical trial is a *Dose Escalation* trial in which successive small groups of the subjects/patients are given successively higher doses of the treatment until some of the subjects/patients experience the unacceptable side effects. In the most Phase-I trials there are 3-6 patients in each dose group. The first group of the patients in the trial typically get a rather low dose. If unacceptable side effects are not seen in the first group, the next group gets a higher dose. This continues until a maximum tolerable dose is reached.

The subjects/patients in the first dose group of a Phase-I trial of a new drug are the first humans ever to get that drug. Such a trial is a truly experimental treatment. The safety of the subjects/patients participating in these trials is the paramount consideration in proceeding to the clinical trials in man. This phase includes the trials designed to assess the safety[17], tolerability, pharmaco-kinetics, and pharmacodynamics of a therapy.

It's important to realize that individual patients are only treated at a single dose level, although they may receive several treatments at that dose level. It's also important to understand that the few patients who are treated at a dose above the maximum tolerated dose may not have the serious problems.

[17] The safety (Pharmacovigilance) is the detection, assessment, understanding, and prevention of the adverse effects, particularly the long term and short term side effects of the medicinal products.

Some Phase-I clinical trials test a new combination of the drugs rather than a new drug. Perhaps a drug is being added to a standard treatment already known to have some effectiveness, or perhaps two active drugs are being tested in the combination in the hopes that the results will be superior to those with either the drug alone. The combinations in the Phase-I trials can involve the drugs which are not yet approved for the general use. Typically the new drug, though not approved, has already shown the promising results by itself. The Phase-I clinical trials of the combinations are still the dose escalation studies, but because the side effects of the individual drugs are known, the investigators have a better idea what doses are likely to be tolerable, what the side effects are likely to be, and what doses may be required for the efficacy. If there is an effective standard treatment for a type of the cancer and the situation it is required that the patient already received the standard treatment before participating on a Phase-I clinical trial. The exception is when the trial treatment is a variation on the standard treatment.

3.1.1. Dose Escalation

The calculation of the right dose for an investigational product is very important step before starting the clinical trials. In the Phase-Ia clinical trials for the dose escalation the shape of the dose-response curve from the non-clinical studies has to be taken into account. The dose increases must proceed with the caution because the initial dose would have been low and there may be a steep dose-response curve. The choice of the next dose level has to include some estimate of the potential pharmacodynamic effects and adverse effects.

3.2. Phase-II Clinical Trials

Once the initial safety of the therapy has been confirmed in the Phase-I, Phase-II trial tests the ability of the treatment to produce the measurable results, as well as to continue the Phase-I assessments, in a larger group of the patients (typically 20-300), all with the same disease status. A Phase-II clinical trial is the first test directed at any measure of the efficacy. Many, but not the all Phase-II clinical trials are multi-centre trials.

- The One Stage Design. In the simplest Phase-II clinical trial, a pre determined number of the patients with the same type of the disease status will receive the treatment at the dose determined in the prior Phase-I clinical trial.
- The Two Stage Design. Many Phase-II clinical trials will be conducted in the two stages. In the two stage design, after a pre-determined number of the patients have been treated, the trial will be paused, and the response rate will be evaluated. If the response rate is less than a pre specified minimum goal. It will be concluded that the treatment is not worth pursuing, and the trial will be ended. Otherwise, the trial will be restarted and a pre-determined number of the additional patients will be included for the determination of the efficacy rate.

3.3. Phase-III Clinical Trials

Phase-III clinical trials are randomized controlled trials on the large patient groups (300–3,000). Depending on the study condition the patient number can be more. The Phase-III clinical trials are aimed at being the definitive assessment of the efficacy of the new therapy, in comparison with the current 'Gold Standard' treatment. The Phase-III clinical trials are the most expensive, time-consuming, and difficult trials to design and run. Because the survival is

the usual endpoint, they can take a long time to accrue the planned number of the patients and follow them for long enough to get a meaningful result.

The Phase-III clinical trials compare two treatments for a particular kind of the disease. Typically an experimental treatment is compared to a standard treatment. The usual objective is to see if the new treatment produces better effect than the old one. In some cases the objective is to show that a treatment with the lesser side-effects is at least as good as the standard treatment. In this case, the treatment with the lesser side effects doesn't have to produce the better effects than the standard treatment to be considered an advance. It only has to be as good. The standard Phase-III clinical trial randomizes the patients between the treatments being tested in the trial.

3.4. Phase-IV Clinical Trials

The Phase-IV clinical trials involve the post-launch safety surveillance and the ongoing technical support of a drug. The pharmaceutical companies have several objectives to conduct the Phase-IV clinical trials:

- To compare a drug with the other drugs already in the market,
- To monitor a drug's long-term effectiveness and impact on a patient's quality of life,
- To determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies, and
- To detect any rare or long-term adverse effects over a much larger patient population and timescale than was possible during the initial clinical trials.

The significant adverse effects detected by the Phase-IV clinical trials may result in the withdrawal or restriction of a drug.

3.5. Academic Clinical Trials

The Academic clinical trials are a very important component of the health system. They are beneficial for the patients and discovering new drugs. The Academic clinical trials run at the academic sites (include Medical Schools, Academic Hospitals of the Universities). The funding of the academic studies comes from the different groups with an interest in the clinical trials. These groups include:

- The pharmaceutical or biotech companies,
- The health authorities,
- The researchers, and physicians, and
- The patient organisations and associations who want faster access to the cutting-edge treatments.

3.6. Off-Label Use of Approved Drugs

The off-label use of a drug simply means the drug is prescribed for a different specific purpose than the purpose for which it was approved by the regulatory boards e.g. EMEA, FDA. The physicians can legally prescribe the drugs for the off-label uses. This is very common in the medicine, especially in the cancer medicine.

4. Procedure for Performing Clinical Trial

The activities for the clinical trials can be defined in three steps:

- Activities before the start of a clinical trial.
- Activities during the conduction of a clinical trial.
- Activities after the termination of a clinical trial.

4.1. Start of Clinical Trials

Before commencing any clinical trial, the sponsor has the different duties. Also, the sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion. Further, the competent authority has to give the permission to the sponsor after the submission of a valid request for the authorisation in which the sponsor plans to conduct the clinical trial. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor. After the planning a clinical trial the sponsor may prepare an investigational protocol. Before starting the clinical trials the sponsor must fulfil the following duties:

- The site selection, where the clinical trials have to be performed,
- The choose of the principal Investigator for each country,
- The request of the unique identification number for the clinical trial (Europe),
- The positive opinion of the ethics committee from each country,
- The permission by the competent authority, and
- The choose of the investigators participating in the trial,
- The site initiation visit.

4.1.1. Site Selection

The purpose of the site selection is to assess if the site is interested to participate on the trial and if the site has the capability to perform this trial.

4.1.1.1. Information on Clinical Site

In the first step the investigator has to know in which clinical trial he will be involved. For these purpose he has to receive at least the synopsis of the planned clinical trial. Before given the synopsis to the investigator he has to sign the "Confidentiality Agreement". After receiving the Confidential Agreement the sponsor will provide the investigator with synopsis of the trial and the site selection form.

4.1.1.2. Site Selection Form

In the site selection form the investigator will provide the sponsor with the prospective data about the expected subject inclusion at the site, and the information about the infrastructure, and the ongoing clinical trials at the site.

4.1.1.3. Pre-study Visit

The purpose of a pre-study visit is to select the investigators and investigative sites. The objective is to determine whether the investigator is qualified by the training and experience to conduct the investigation. The second part of a pre-study visit is to investigative the site that means to perform an inspection of the physical ability of the site. It should be clean, orderly, and adequate. Also, the monitor has to verify the existence of a private area for:

- The obtaining the informed consent,
- The delivering the subject care,
- The conducting the subject interviews, and

- The completing the administrative procedure.

Confidentiality Agreement

This letter of agreement between "**Investigator Name**" and "**Sponsor Name**", effective as of "**Date of Agreement**", shall govern the use and disclosure of the information about the clinical trial "**Title of the Study**" by you, and your clinical trial staffs and employees. It is your responsibility to inform your clinical trial staffs and employees of the proprietary nature of the provided information and to use all reasonable efforts to ensure that they do not disclose the provided Information to a third party or use the provided Information except as permitted herein.

The provided information are extended of the confidential business, scientific, technical, or other ideas, and information, whether disclosed by "**Sponsor Name**", its agent, or observed by the recipient including, without the limitation, the information relating to the planned clinical trial. The furnishing of the provided Information shall not constitute any grant, option, or license to the recipient under any patent or other rights now or hereinafter.

The recipient shall not use the provided Information except for the completion of the trial questionnaires, and shall not disclose the provided information to others without the express written permission, except that the recipient shall not be prevented from using or disclosing the provided information:

- That is lawfully obtained by recipient from the sources independent who have a lawful right to disclose such information,
- That is required to be disclosed pursuant to a law, regulation, or other legal proceeding, provided:

a. The recipient first provides "**Sponsor Name**" with the reasonable advance

b. Any disclosure hereunder is limited in the scope and the recipients to that which is required by such legal proceeding,

- That the recipient can demonstrate by the written records was previously known to the recipient, or
- That is now the public knowledge, or becomes the public knowledge in the future, other than through the recipient's acts or omissions in the violation of this Confidentiality Agreement.

The obligations of the confidentiality set forth in this agreement shall remain in effect for ten years from the date of the each disclosure.

Any changes to the terms of this Confidentiality Agreement made by you without the prior written agreement are null and void.

Accepted and Agreed

By ---------- ----------

Investigator Name and Title Date

4.1.1.4. Required Documents

After ensuring that the site is qualified for the participation in the clinical trial the sponsor has to receive the following documents from the site for the submission to the ethic committee, and the competent authorities:

- The curriculum vitae (CV) of all site staffs and their experience in the performing clinical trials.
- The signed protocol agreement.
- The signed GCP-agreement by the investigator and all sub-investigators.
- The signed FDA-form 1571 in the case that the trial has been submitted to the FDA.
- The financial disclosure form.

4.1.1.3.1. GCP-Training

The investigators shall be informed well about the ICH-GCP. This knowledge has to be based by the training. It can be performed internal or external. Also, the investigators shall document the internal training adequately.

4.1.1.3.2. Curriculum Vitae

The CV is a detailed written description of one's education and experience. It is used to seek the positions in the academic or educational environments. Before starting the clinical trials the investigators have to provide the sponsor of the clinical trial with an updated CV, which may contain at least detailed information about their academic position, and their experience in the performing clinical trials.

4.1.1.3.3. GCP-Agreement

Before starting a clinical trial the investigators have to provide the sponsor of the trial with a statement that their activities during the clinical trials will be in accordance to the ICH-GCP-Guidelines.

Investigator Protocol Agreement

Protocol number and version: ……..…… Protocol date: ……

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Address of Institution: _____

_____

_____

☐ Principal Investigator ☐ Co-Investigator

Print Name _____

Signature _____ Date _____

4.1.1.3.4. Protocol Agreement

Before starting a clinical trial the investigators have to provide the sponsor of the trial with a statement that they have read the protocol, and agree with the discussed points in the trial protocol.

4.1.1.3.5. FDA form 1572

The FDA form 1572 is a statement of the investigator that he/she will abide by the federal guidelines set forth in the Code of the Federal Regulations for the use of the drugs in an investigational setting. The initial IND (investigational new drug) submission and each subsequent submission to the IND have to be accompanied by a FDA form 1571. It has to be submitted in triplicate (the original and two photocopies are acceptable).

http://forms.psc.gov/forms/FDA/FDA-1572.pdf

FINANCIAL DISCLOSURE

Sponsor …….. Protocol Title …….
Principal Investigator Name ……..

Please indicate by the marking Yes or No if any of the financial interests or arrangements with the Sponsor apply to you, your spouse, or dependent children:

Any ownership interest, stock options, or other financial interest in the Sponsor whose value cannot be readily determined through the reference to the public prices. ☐ Yes ☐ No
If yes, please specify: ……

Any equity interest in the Sponsor such as bearer shares, non-voting equity security, or American Depository Receipts that is equal to or exceeds $50,000. ☐ Yes ☐ No
If yes, please specify: ……

A financial agreement with the Sponsor whereby the value of the compensation could be influenced by the outcome of this study. This includes the compensation that could be greater for the favourable clinical results, compensation in the form of an equity interest in the Sponsor or the compensation tied to sales of the product tested in the above-listed study, such as a royalty interest. ☐ Yes ☐ No
If yes, please specify: ……

Any proprietary interest in the product tested in this study such as patents rights or rights under a patent, trademark, copyright or licensing agreement. ☐ Yes ☐ No
If yes, please specify: ……

The payments received from the Sponsor, since the commencement of this study, which in the aggregate exceeds $25,000. This includes the honoraria, retainers for ongoing consultation, payments for speaking engagements or participation in advisory boards on behalf of the company, compensation in the form of equipment, grants including those to support the investigator initiated research, and payments to your institution to support your activities. It does not include payments for the conducting this study or any other clinical study sponsored by the Sponsor.

☐ Yes ☐ No

If yes, please specify: ……
I certify that the information provided above is correct and complete. Where applicable, I agree that this information may be sent to the other countries where the same level of the data protection may not apply. I understand that I am obligated to amend this statement and notify the Sponsor if there is a change in this information up to one (1) year after the completion of the study.

☐ Principal Investigator ☐ Co-Investigator
Print Name _____
Signature_____ Date _____

4.1.1.3.6. Financial Disclosure Form

In a financial disclosure form the investigator declare that he/she has no financial involvement with the sponsor. Further, he/she will assure that the changes will be announced to the competent authority as soon as possible.

4.1.2. Identification Number for Clinical Trial (EU)

A unique EudraCT number identify each clinical trial. One EudraCT number will be issued per protocol, irrespective of the number of the clinical trial sites or member states involved. Also, a EudraCT number will only be issued once by the system. The EudraCT number is issued to the sponsor by a central function in the system on the submission of the required data to the system. The unique EudraCT number for each clinical trial has the format YYYY-NNNNNN-CC, where:

- YYYY is the year in which the number is issued,
- NNNNNN is a six digit sequential number, and
- CC is a check digit.

Each sponsor registers single or multiple users with the system. The sponsor may delegate the task of submitting the information to the system, to other parties, so the sponsor may register the representatives/authorised parties to act on its behalf but the sponsor retains the ultimate responsibility for the data submitted.

The first part provides the facilities for the obtaining a EudraCT number for a clinical trial. This is a two-step process:

- A security code reference will be obtained as a means of the validating the EudraCT number request, and
- Some simple information about the requestor and the Sponsor's Protocol Code Number of the trial for which the EudraCT number is required.

The EudraCT number has to be used:

- In the submission of the request for the trial to the competent authorities,
- In the submission of the request for the trial to the ethics committees,
- On the study protocol,

- On any amendments,
- On the trial report, and
- On any suspected unexpected serious adverse reactions (SUSAR) reports

for the reports from the trials.

4.1.3. Vote of Independent Ethic committee

The clinical trial on a medical product for the human use has to start after the appropriate Ethic Committee (EC)/Independent Review Board (IRB) has issued a favourable opinion. The EC/IRB shall give its opinion within the scope of its responsibilities. There is one single EC/IRB per country on a proposed multi-centre trial without excluding the possibility of rejecting it at the specific site.

4.1.3.1. Timetable of EC/IRB

The EC/IRB has a maximum of 60 days from the date of the receipt of a valid application to give its reasoned opinion to the applicant and the competent authority. Within the period of the examination of the application for an opinion, the EC/IRB may send a single request for the information supplementary to that already supplied by the applicant.

No extension to the 60-day period is permissible except in the case of the trials involving the medicinal products for the gene therapy, somatic cell therapy, or medicinal products containing the genetically modified organisms. In these cases, an extension of a maximum of 30 days is permitted. For these products, this 90-day period may be extended by a further 90 days in the event of the consultation of a group or a committee in accordance with the regulations and

procedures of the Member States concerned. In the case of a xenogenic[18] cell therapy, there is no time limit to the authorisation period.

Timelines for EC/IRB

Product	Maximum of time
Standard products	60 days
Gene therapy	90 days
Genetically modified organisms	90 days
Somatic cell therapy	90 days
External need of consultation	+ 90 additional days
Xenogenic cell therapy	no limit in time

4.1.3.2. Application Form

The application form comprises two modules.

- **The first module** (Module 1) contains the information on the administration of the trial, and the identifying the investigator for the multi-centre trials. There will also be the information on the investigational medicinal products (see Appendix).
  - The list of the principal investigators and all other sites than plan to participate in the conduct of the trial for the multi-centre trials
  - The recruitment of the additional sites in a multi-centre trial after the EC/IRB give a opinion on the qualification of the new principal investigator, the provisions for the insurance, and the quality of the facilities.
- **The second module** (Module 2) contains the headings that might be helpful for the review by the EC/IRB (see Appendix).

[18] The xenogenic cells mean that the cell originates from the outside an organism and has to be introduced. The xenotransplantation is the transplantation of the cells, tissues, or organs from one species to another such as from the pigs to the humans. Such cells, tissues or organs are called the xenografts.

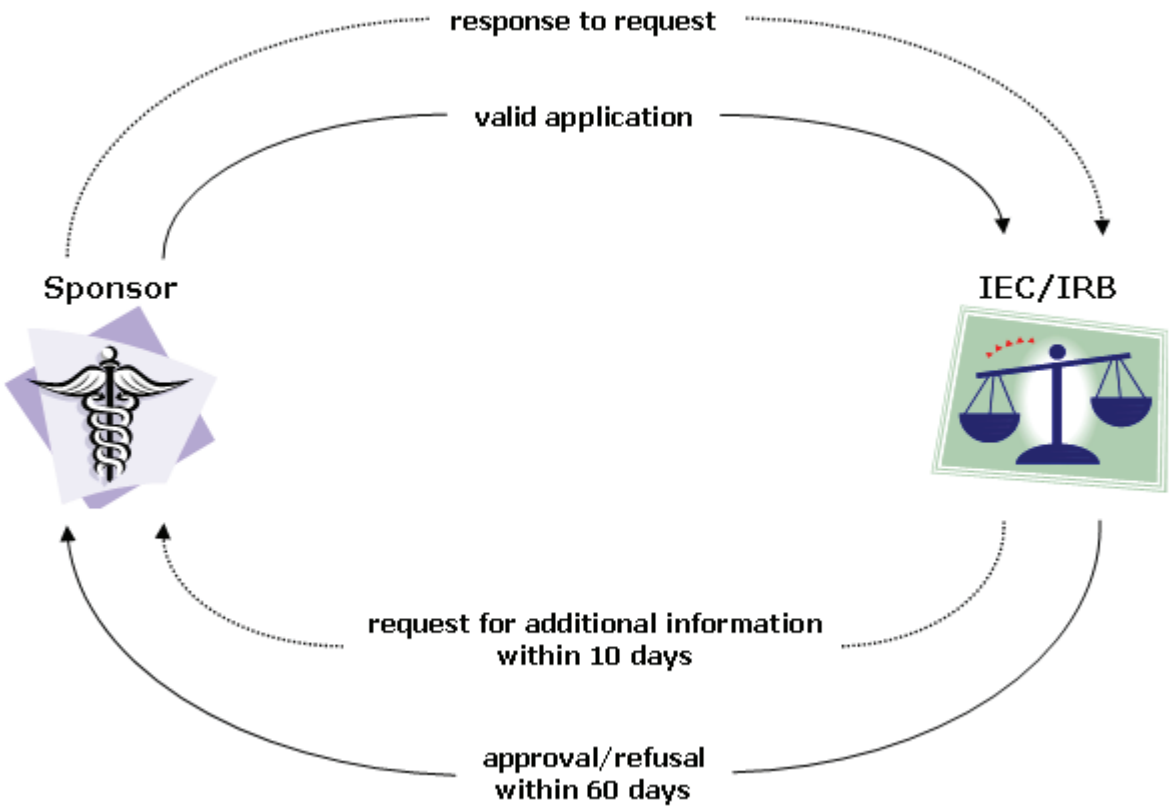
4.1.3.3. Application Documents

The applicant for an EC/IRB opinion can be the sponsor or his legal representative. The application to the EC/IRB is considered to be valid if it fulfils the requirements. If that is the case the applicant will be informed and the review period starts. If the application is not valid the applicant will be informed of the deficiencies. Application form has to be signed by the sponsor or the sponsor's legal representative.

The following documents have to be provided to the EC/IRB:

- The covering letter,
- The Module 1,
- The Module 2,
- The Application form and EudraCT printed form giving the trial number,
- The investigator's brochure,
- The complete trial protocol with amendments,
- The protocol summary,
- The informed consent form,
- The subject information leaflet,
- The insurance details,
- The copy of the early EC/IRB opinion where available,
- A list of the competent authorities to which the application has been submitted and the details of the decision,
- If the applicant is not the sponsor, a letter of the authorisation enabling the applicant to act on behalf of the sponsor,
- A copy of the authorisation for the contained use or release of the genetically modified organisms (when applicable and available),
- The qualification of the principal investigator,
- The qualification of all investigators,

- The qualification documents of all investigational sites, and
- The Financial Disclosure form.



4.1.3.4. Covering Letter

The sponsor or his legal representative has to submit and sign a covering letter with the application. Its heading has to contain the EudraCT number and the sponsor protocol number with a title of the trial. The text has to draw the attention to any special issues related to the application such as the special trial populations, the unusual investigational medicinal products, the unusual trial designs etc. and indicate where the relevant information is in the application.

4.1.4. Request for Authorisation of Clinical Trial in Europe

The review by the competent authority can take place sequentially or in parallel with the review by the EC/IRB. The applicant for a competent authority opinion can be the sponsor or the sponsor's legal representative. If the applicant is not the sponsor, they has to enclose a letter from the sponsor authorising the applicant to act on their behalf. The application form comprises one module which is the same as the application form that has been used as part of the submission to the EC/IRB. The applicant must submit a valid request for the authorisation to the competent authority. The sponsor has to provide the competent authority with a copy of the opinion of the EC/IRB as soon as it is available. When an EC/IRB responsible for giving a single opinion gives an unfavourable opinion the sponsor has to inform the competent authority. If the application is not valid the applicant will be informed of the deficiencies. The application to the competent authority is considered to be valid if it fulfils the requirements. If that is the case the applicant will be informed and the review period starts.

The following documents have to be provided to the competent authority:

- The covering letter,
- The Module 1,
- The Application form and EudraCT printed form giving the trial number,
- The investigator's brochure,
- The complete protocol with the amendments to date,
- The protocol summary,
- The informed consent form,
- The subject information leaflet,
- The insurance details,

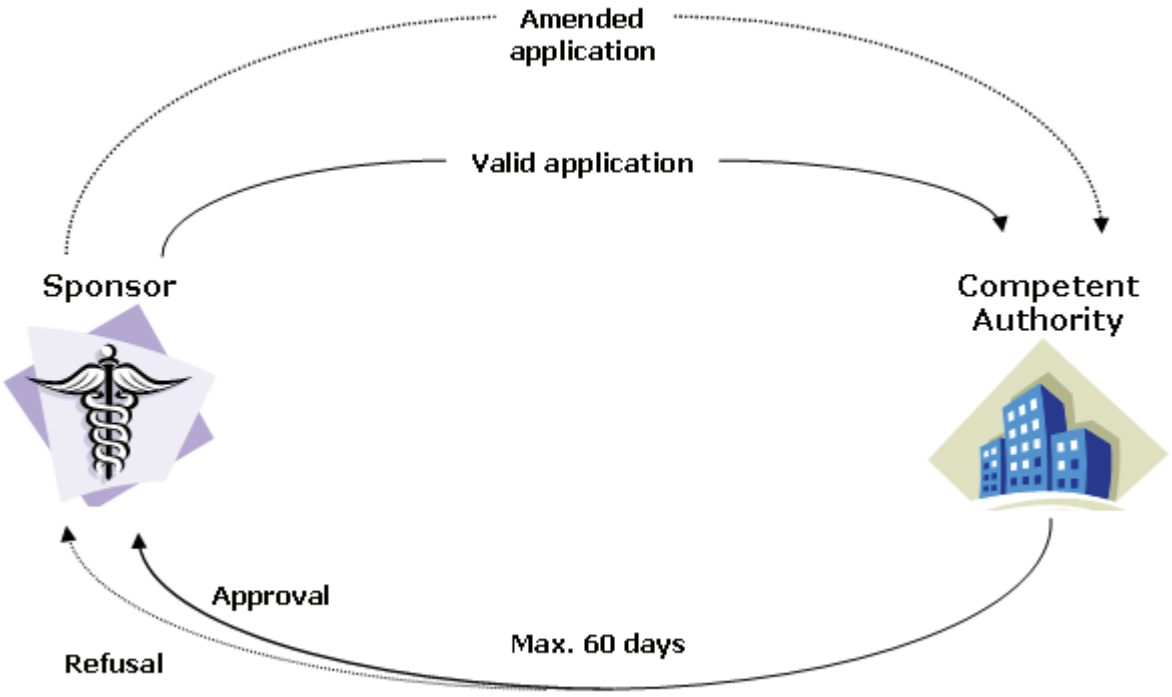
- A copy of EC/IRB opinion where available,
- The manufacturing licence,
- The declaration of the qualified person that the manufacturing site works in compliance with the EU GMP,
- A list of the competent authorities to which the application has been submitted and details of their decisions,
- If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor,
- A copy of the authorisation for the contained use or release of the genetically modified organisms (when applicable and available),
- The investigational medicinal product dossier,
- The qualification of principal investigator,
- The qualification of all Investigators,
- The qualification of all investigational sites,
- The financial agreement, and
- The financial disclosure form.

Written authorisation is required before the commencement of the clinical trials. If the competent authority notifies the sponsor of the grounds for the non-acceptance, the sponsor has, on one occasion only, to amend the content of the request in order to take due account of the grounds given. The consideration of a valid request for the authorisation by the competent authority will be carried out as rapidly as possible, and does not exceed 60 days.

The competent authority is responsible for:

- The reviewing the clinical trial documents,

- The reviewing the financial agreements between the sponsor and the principal investigator or site, and
- The inspection (auditing) the clinical trial.



4.1.4.1. Covering Letter

The sponsor or his legal representative has to submit and sign a covering letter with the application. Its heading has to contain the EudraCT number and the sponsor protocol number with a title of the trial. The text has to draw the attention to any special issues related to the application such as special trial populations, the unusual investigational medicinal products, the unusual trial designs etc. and indicate where the relevant information is in the application.

4.1.4.2. Application Form

The application form must uniquely identify the clinical trial, the organisations, and key individuals responsible for the conduct of the trial,

such as the contact person and the name of the investigator. The sponsor has to print the completed form, sign and date it, and send it as part of the application to the competent authority.

Sponsor's signature will confirm:

- That the provided information is complete,
- That the attached documents contain an accurate account of the information available,
- That in their opinion it is reasonable for the proposed clinical trial to be undertaken,
- That any information is provided to both the competent authority and EC/IRB, and
- That the EC/IRB opinion is based on the same data.

4.1.5. Request for Authorisation of Clinical Trial by FDA

When a sponsor submits a clinical trial to the FDA as part of the initial application for an IND, the FDA has thirty days to review the application and place the trial on "hold" if there are any obvious reasons why the proposed trial should not be conducted. Also, the request for the authorisation a clinical trial by the FDA is called the IND program. The IND program means that a pharmaceutical company obtains the permission to ship an experimental drug to the investigators of the clinical trial before a marketing application for the drug has been approved. The FDA reviews the IND for the safety to assure that the research subjects will not be subjected to the unreasonable risk. A clinical trial also requires an IND if it is intended to support a:

- New therapeutic indication,
- Change in the approved route of the administration,
- Change in the approved dosage level,

- Change in the approved patient population, and
- Change in the promotion of an approved drug.

The IND application has to contain information in three broad areas:

- The Investigator's Brochure, which contain the data from the preclinical studies, and the early human studies with this substance,
- The information about the chemical structure, stability, activity, and properties,
- The information about the manufacturing process,
- The study protocol,
- The information on the qualifications of the clinical investigators,
- The commitment to obtain the informed consent from the trial subjects, and
- The commitment to obtain the review of the trial by an EC/IRB.

4.1.5.1. New Drug Application Form

The FDA form 1571 is the application form for the new investigational drugs. It will be submitted by the sponsor. Also, if a pharmaceutical company will be supplying the investigational drug, but itself will not be submitting the IND, the company is not the sponsor. It is necessary for the sponsor to submit at least the following information with an IND:

- The manufacturing and controls information,
- The pharmacology and toxicology data, and
- The data from the prior human studies.

In the cases that the information previously has been submitted to the FDA, and the sponsor of the previously submitted information provides a letter authorizing the FDA to refer to the information, the letter of the authorization including the file identification has to be:

- Submitted to the authorizer's application, and
- Included in the initial submission of the new sponsor's IND.

For a pharmaceutical company, the name of the person responsible for the monitoring the conduct of the clinical investigation, and reviewing and evaluating the safety information, has to be entered. In the case of the investigator initiated trials (Sponsor-Investigator) the investigator has this responsibility.

For an IND sponsored by a pharmaceutical company, or research organization, the sponsor's authorizing representative has to be named and sign the form. In the case of the investigator initiated trials the investigator has to be named and sign the form.
http://www.fda.gov/opacom/morechoices/fdaforms/1571es.pdf

4.1.6. Announcement of Starting Clinical Trial

Before starting the clinical trial at the trial site the competent authority has to be announced about the conduction of the trial on that site. This announcement is the responsibility of the investigator which can be delegated to the trial's sponsor.

4.1.7. Study Initiation Visit

The purpose of a study initiation visit is to train the investigator and the study staff in:

- The study protocol,
- The applicable regulations,
- The administration of the investigational product, or use of the device, and
- The other sponsor requirements.

The monitor has to conduct an initiation visit any time within a month or so of starting the study. The study initiation visit takes some time. It depends on the investigator, and the site knowledge about the initiated study. The monitor hat to plan a page-by-page review of:

- The study protocol,
- The informed consent forms,
- The trial file,
- The CRF,
- The investigator's brochure, and
- Any other study related procedures.

4.2. During Clinical Trials

During conducting the clinical trials the sponsor has to submit any changes of the trial protocol or safety reasons to the EC/IRB and the competent authorities.

4.2.1. Submission of Documents to EC/IRB

After starting the clinical trial certain documents have to be submitted to the EC/IRB for the consideration or the information during the conduct of the trial. If the amendments to the study protocol are required after the start of the trial, the EC/IRB is required to give its opinion on the proposed changes. Also, all necessary documents have to be submitted to the EC/IRB.

4.2.1.1. Timetable of EC

In Europe the EC/IRB has to give an opinion on a proposed substantial amendment within 35 days. The amendment can be implemented after 35 days from the receipt of a valid notification of an amendment.

4.2.2. Competent Authority

After starting the clinical trial the certain documents have to be submitted to the competent authority for the consideration or the information during the conduct of the trial. If the amendments to the study protocol are required after the start of the trial, the competent authority is required to give its opinion on the proposed changes. Also, all necessary documents have to be submitted to the competent authority.

4.2.2.1. Timetable of Competent Authority

If the competent authority has not raised the grounds for the non-acceptance of an amendment it has to be implemented after 35 days from the receipt of a valid notification. However, if the competent authority consults a group or committee, the time for the response could be extended. In this case the competent authority will notify the sponsor of the duration of the extension.

4.2.3. Monitoring During Clinical Trial

The routine monitoring visits are the heart of the study monitoring. The Monitor has to read the last monitoring report, the previously reported serious adverse events (SAE's) and all other relevant correspondence.

4.3. End of Clinical Trials

The definition of the end of the trial has to be provided in the study protocol and any change to this definition for whatever reason has to be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this have to be justified in the protocol.

4.3.1. Termination of Clinical Trial by Data Safety Monitoring Board

The protection of the patient safety is the primary mandate of the Data Safety Monitoring Board (DSMB). If the serious adverse events of a particular type are more common in the experimental arm compared to the control arm, the DSMB would strongly consider the termination of the study. This evaluation will be made by the consideration of the risk/benefit quotient. Further, the DSMB would consider the termination of the study by overwhelming the benefit of the experimental arm. Also, in the case of undeniably superior of the experimental arm to the control arm the DSMB may recommend the termination of the trial. The statistical proof needs to be very high indeed. The other aspect of the early termination can be futility. In the case of the identical results in experimental and the control arm there is in no one's interest to continue this trial.

4.3.2. Premature Close-Out of Site

A premature close-out of a trial site can occur in the following cases:

- If the investigator has not included any subjects after a reasonable period of the time mutually agreed in the trial,
- In the event of the breach by the investigator at least one of the following cases,
  - A fundamental obligation under the agreement,
  - The breach of the applicable laws and obligations,
  - The breach of the ICH-GCP guidelines, and
- Due to the written request of the investigator.

4.3.3. Premature Discontinuation of Clinical Trial

A premature discontinuation of the clinical trial can occur in the following cases:

- In the event that the results of the clinical trial do not appear to be scientifically convincing,
- If the results and collected data lead to a doubt about the benefit/risk ratio,
- If the aim of the clinical trial has become outdated,
- If the aim of the clinical trial is no longer of the interest, and
- If the total number of the trial subjects are included earlier than expected.

4.3.4. Termination of Clinical Trial on EC

The sponsor has to notify the EC/IRB within 90 days about the termination of the clinical trial. In the case of an early termination of the trial or temporary halt by the sponsor the EC/IRB has to be notified within 15 days, and a detailed written explanation of the reasons for the termination/halt has to be given.

At the end of the trial (on all sites in a multi-centre trial) the sponsor has to provide the EC/IRB with a summary of the trial's outcome. The principal investigator has to have access to the recorded data to ensure the accuracy, completeness and timelines. The report has to be the same as the one forwarded to the competent authority.

If after the termination of a trial the risk/benefit analyses have changed, the new evaluation has to be provided in the case it will be an impact on the planned follow up of the subjects who have participated in the trial. If so, the actions needed to protect the subjects have to be described.

4.3.5. Termination of Clinical Trial on Competent Authority

The sponsor has to notify the end of the trial within 90 days of the end of the clinical trial. Whenever a trial is terminated early the sponsor has to notify the competent authority within 15 days and clearly explain the reasons. If the sponsor decides not to commence initially or not to recommence the trial after halting it, they have to notify the competent authority. They have to submit a letter that has to identify the study protocol, its sponsor's protocol code number, the EudraCT number, and provide a brief explanation of the reasons for not starting the trial or for ending it.

At the end of the trial the sponsor is required to notify the competent authority of the end of the trial, or of its early termination. The competent authority enters the data on the receipt of the declaration of the end of the trial. The sponsor has also to provide a summary of the clinical trial report within one year of the end of the trial to the competent authority as required by the GCP guideline.

4.3.6. Closeout Visit

The monitor's final responsibility is the study closeout visit. The purpose of this visit is to resolve the remaining issues at the end of the study and bring the trial to a close. During the closeout visit, the monitors will review the investigator's file for the last time, making sure it is complete and up-to-date. They will balance the device or the drug accountability log, and ship the remaining study articles to the sponsor. The study documents have to be prepared for the archiving for at least 15 years at the site.

4.3.7. Final Report

After the termination of the clinical trial the sponsor has also to provide a summary report within one year of the end of the trial to the competent authorities. If a new event occurs after the termination of the trial that is likely to change the risk/benefit analysis of the trial and could still have an impact on the trial participants, the sponsor has to notify the competent authorities concerned and provide a proposed course of the action.

5. Ethics Committee

The ethics has his origin in the Ancient Greek, where the “ethikos” meant “arising from habit". The ethics is the study of the value or quality, and covers the analysis, and employment of the concepts, and analysis. The ethics is divided into three primary areas:

- The study of what ethicality is (meta-ethics),
- The study of what the ethical truths there are and how they are known (normative ethics), and
- The study of the use of the ethical knowledge (applied ethics).

Many of the ethical issues that arise in the human experimentation — such as those surrounding the informed consent, confidentiality19 and the physician’s duty of the care to the patient — overlap with ethical issues in the clinical practice. In the clinical practice, the physician has a clear obligation to the patient. In the research the researcher has an obligation to ensure that the clinical trial findings are valid and replicable, and this has the implications for the design and execution of the clinical trial. Also, the clinical trial has to be designed in such a way:

- That the research question is answered reliably and efficiently,
- That sufficient numbers of the patients/subjects are enrolled in a reasonable period, and
- That the clinical trial participants comply with their allocated treatment.

[19] The collection of the personal information might pose a legal or social risk to the participants, it is important to ensure that this information will be kept confidential. By incorporating the measures to protect confidentiality, harm to the participant can be minimized.

The predominant ethical framework for performing the human experiments was set out by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in the Belmont Report in 1979. This report articulated 3 guiding principles for the research:

- **The respect for the persons** requires that the choices of the autonomous individuals be respected and that the people who are incapable of making their own choices be protected. This principle underlies the requirement to obtain the informed consent from the clinical trial participants and to maintain the confidentiality on their behalf.
- **The beneficence** requires that the participation in the research is associated with a favourable balance of the potential benefits and harms.
- **The justice** entails an equitable distribution of the burdens and benefits of the research.

To ensure that the ethical issues in the case of the trial subjects have been considered there is a need to have the EC/IRB. It is an appropriately constituted group that has been formally designated to review and monitor the biomedical and behavioural research involving the human subjects. The EC/IRB has the authority to approve, require the modifications, or disapprove the research. An EC/IRB has the duty to critical oversight the research conducted on the human subjects.

5.1. History of EC/IRB

The EC/IRB was developed in the direct response to the research abuses earlier in the twentieth century. Three of these notorious abuses were:

- The experiments of the Nazi physicians that became a focus of the War Trials (Nuremberg Trials),

- The Tuskegee Syphilis Study[20] (an unethical and scientifically unjustifiable project conducted between 1932 and 1972 by the U.S. Public Health Service on the poor, illiterate black men in the rural Alabama, and
- The Hepatitis A trial was a notorious study at the Willowbrook State School for the Retarded in New York, in which the researchers intentionally infected the mentally disabled children with the Hepatitis A.

5.2. Composition of EC/IRB

The EC/IRB is an independent body consisting of the healthcare professionals and non-medical members. Each EC/IRB has the Standard Operating Procedures (SOPs), which give the exact detail of the committees' composition, the meeting frequency, the officer's duties, the appointment of the substitute members, the access to the documents, the decision-making, the statistics, and so on.

5.2.1. EU

Due to the EU directive each Member States has to establish one or more EC/IRB that is responsible for giving an opinion before a clinical trial commences. It consists of the healthcare professionals and non-medical members.

5.2.2. FDA

Based on the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (1974-1978), the Department of Health and Human Services revised and expanded its regulations for the

[20] The Tuskegee Syphilis Study was a clinical study, in which 399 poor African American sharecroppers were denied the treatment for the Syphilis. The trial subjects had participated without given the informed consent. Further, they were not informed of their diagnosis.

protection of the human subjects “45 CFR part 46” in the late 1970's and early 1980's. In 1978, the Commission’s report “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” was published. It was named the Belmont Report, for the Belmont Conference Centre, where the National Commission met when first drafting the report. Due to §46.107 of this regulation:

- Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of the research activities commonly conducted by the institution.
- The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including the consideration of race, gender, and cultural backgrounds and the sensitivity to such issues as the community attitudes, to promote respect for its advice and counsel in the safeguarding the rights and welfare of the human subjects.
- The IRB shall have the professional competence necessary to review the specific research activities.
- The IRB shall be able to ascertain the acceptability of the proposed research in terms of the institutional commitments and regulations, applicable law, and standards of the professional conduct and practice.
- The IRB shall therefore include the persons knowledgeable in these areas. If an IRB regularly reviews the research that involves a vulnerable category of the subjects, such as the children, prisoners, pregnant women, or handicapped or mentally disabled persons, the consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.
- Every non discriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration

of the qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender.

- No IRB may consist entirely of the members of one profession.
- Each IRB shall include at least one member whose primary concerns are in the scientific areas and at least one member whose primary concerns are in the non scientific areas.
- Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
- No IRB may have a member participate in the IRB initial or continuing review of any project in which the member has a conflicting interest, except to provide the information requested by the IRB.
- An IRB may, in its discretion, invite the individuals with the competence in the special areas to assist in the review of the issues which require the expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

5.2.3. ICH-GCP

According to the ICH-GCP-Guideline the EC/IRB should consist of a reasonable number of the members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the EC/IRB should include:

- At least five members,
- At least one member whose primary area of the interest is in a non-scientific area, and
- At least one member who is independent of the institution/trial site.

The EC/IRB members who are independent of the investigator and the sponsor of the trial should vote/provide the opinion on a trial-related matter. Further, a list of the EC/IRB members and their qualifications should be available.

5.3. Responsibility of EC/IRB

According to the ICH-GCP guideline an EC/IRB should safeguard the rights, and safety of all trial subjects. The special attention should be paid to the trials that may include the vulnerable subjects, such as the pregnant women, children, prisoners, the elderly, or the persons with the diminished comprehension. Furthermore, the EC/IRB only approves the research for which the risks to the subjects are balanced by the potential benefits to the society:

- For which there is a *bona fide* the informed consent process for the participants, and
- For which selection of the subjects affords the opportunities to participate for all eligible populations.

According to the ICH-GCP guideline the responsibilities of the EC/IRB before, and during the clinical trial are:

- To protect the rights, safety and well being of the subjects involved in a clinical trial, and
- To provide the public assurance of that protection by expressing an opinion:
  - On the study protocol,
  - On the suitability of the investigators involved in the trial,
  - On the adequacy of the facilities, and
  - On the methods, and documents to be used to inform the trial subjects and to obtain their informed consent.

The EC/IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- The approval/favourable opinion,
- The modifications required prior to its approval/favourable opinion,
- The disapproval/negative opinion, and
- The termination/suspension of any prior approval/favourable opinion.

According to the ICH-GCP guideline the EC/IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the EC/IRB requests. Further, the EC/IRB should conduct continuing the review of each ongoing trial at intervals appropriate to the degree of the risk to the human subjects, but at least once per year.

5.4. Risks and Benefits Assessment by EC/IRB

Before approving a clinical trial the EC/IRB has to weigh the foreseeable risks and inconveniences against the anticipated benefit for the individual trial subjects, other and the future patients. Also, the EC/IRB and the competent authority have to consider this requirement before approval is given.

5.5. Elements of Review by EC/IRB

The primary task of an EC/IRB lies in the review of the research proposals and their supporting documents, with the special attention given to the informed consent process, documentation, and the suitability and feasibility of the protocol. The following points have to be considered, as applicable:

- The study protocol

- The scientific design and conduct of the study
- The appropriateness of the study design in relation
  - To the objectives of the study
  - To the statistical methodology
  - To the potential for reaching the sound conclusions with the smallest number of the research participants
- The justification of the predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities
- The characteristics of the study population
- The justification for the use of the control arms
- The inclusion criteria for the research participants
- The exclusion criteria for the research participants
- The care and Protection of the research participants
- The criteria for prematurely withdrawing the research participants
- The criteria for suspending or terminating the research

➢ The suitability of the investigator's qualifications and experience for the proposed study

➢ The adequacy of the involved trial site

- The supporting staff
- The available facilities
- The emergency procedures

➢ The adequacy of monitoring and auditing the conduct of the research, including the constitution of a data safety monitoring board

➢ The manner in which the results of the research will be reported and published

➢ The recruitment of the research participants

- The informed consent process
  - The description of the process for obtaining the informed consent
  - The adequacy, completeness, and understand ability of the written information to be given to the research participants
  - The clear justification for the intention to include in the research
  - The individuals who cannot consent, and a full account of the arrangements for obtaining the consent or authorization for the participation of such individuals
- Any plans to withdraw or withhold the standard therapies for the purpose of the research, and the justification for such action
- The medical care to be provided to the research participants during and after the course of the research
- The adequacy of the medical supervision
- The steps to be taken if the research participants voluntarily withdraw the consent during the course of the research
- The criteria for the extended access to the use of the study products to the research participants following the research
- The arrangements for informing
  - The research participant's
  - The general practitioner
  - The procedures for seeking the participant's consent to do so
- The compensations for the research participants
- The insurance and indemnity arrangements
- The provisions for the compensation in the case of the injury/disability/death of a research participant
- The protection of the research participant confidentiality

- The measures taken to ensure the confidentiality and security of the personal information concerning the research participants

5.6. Role of EC/IRB during Clinical Trial

During the conduction of a clinical trial the EC/IRB has regularly to be informed in these cases:

- When there are new events relating to the conduct of the trial or the development of the investigational medicinal product where the event is likely to affect the safety of the subjects,
- When there are the reports of the adverse reactions,
- When the trial is halted or terminated early by the sponsor, and
- When the competent authority suspends or prohibits a clinical trial.

Further, the EC/IRB may request the sponsor to submit any other information necessary to fulfil the requirement of the continuing review of the trial according to the ICH-GCP.

5.7. Decision Making Process

For making the decisions on the applications an EC/IRB has to take the following points into consideration:

- The completeness of the documents required for a full review of the application.
- The sufficient time for the review and discussion of an application in the absence of the non-members (e.g., the investigator, representatives of the sponsor) from the meeting.
- To make the decisions only at the meetings where a quorum is present.
- The predefined method for arriving at a decision (e.g., by consensus, by vote).

- To withdraw of the members where there arises a conflict of the interest. In such cases the conflict of the interest has to be indicated to the chairperson prior to the review of the application.
- The negative decision on an application has to be supported by the clearly stated reasons.

5.8. Providing Amendments to EC/IRB

The EC/IRB has to be informed about the substantial amendments to the protocol. Also the sponsor is obliged to submit all relevant documents in support of the amendments. Further, the sponsor can implement the amendments after it has received a favourable opinion of the EC/IRB. In the case of the urgent safety measures to protect the trial subject the amendments can be implemented without a favourable opinion. In this case the sponsor has to inform the EC/IRB as soon as possible about the measures taken, and any plan for the further action. The following points have to be considered by the amendments:

- The submission at the same time to both the EC/IRB and the competent authorities,
- The identifiable (sponsor's amendment code number, version, date, and changes), and signed by the sponsor or the authorised representative of the sponsor, and the principal investigator or the coordinating investigator in the multi-centre trials,
- The reasons for the amendment,
- The submission of all updated documents e.g.
  - Any new version of the Investigator's Brochure, and
  - A new risk benefit analysis, if applicable,
- It is sufficient to submit only the separate pages with the changes, and

- The submission of both the old and new text.

5.9. Adverse Event Reports on EC/IRB

All relevant information about the serious adverse reactions and the new events even likely to affect the safety of the subjects has to be reported to the EC/IRB. During the clinical trial and the follow up period the EC/IRB has to be informed in the case of the death of the trial subjects.

5.10. Single EC Opinion for Each State

According to the Directive 2001/20/EC of the European Parliament and of the Council for the multi-centre clinical trials limited to the territory of a single Member State of EU, the member states has to establish a procedure providing, notwithstanding the number of the EC's, for the adoption of a single opinion for that Member State. In the case of the multi-centre clinical trials carried out in more than one Member States simultaneously, a single opinion shall be given for each Member States concerned by the clinical trial.

5.11. Accreditation of EC/IRB

The Accreditation of the EC/IRB is a new step to ensure the quality. Several countries accredit or inspect the EC/IRB and there is general support for the idea. On this way the self-assessment is a possible model, which is easy to implement. In UK the EC's are provided with the standard self-assessment forms and reference standards. The completed forms will give a preliminary quality status. Following the peer review visit, they will be accredited either definitively or provisionally. The areas for the improvement will be addressed via an agreed work plan.

6. Competent Authority

Before starting the clinical trial the competent authority has to be asked for his opinion. There are different competent authorities which are involved on performing the clinical trial.

6.1. European Medicine Agency (EMEA)

The EMEA is the European agency for the evaluation of the medicinal products. The EMEA has been established in 1995, and is located in London. It operates as a decentralized scientific agency of the EU, and is responsible for:

- The protection and promotion of the human and animal health,
- The coordination of the evaluation and monitoring of the centrally authorized products,
- Developing the technical guidance, and
- Providing the scientific advice to the sponsors.

The EMEA has four different committees:

- The Committee for the Medicinal Products for Human Use (CHMP), which is obliged by the regulation to reach the decisions within 210 days,
- The Committee for the Medicinal Products for Veterinary Use (CVMP), which is obliged by the regulation to reach the decisions within 210 days,
- The Committee on the Orphan Medicinal Products (COMP), which administers the granting development of the drugs which are necessary but would be prohibitively expensive or/and unprofitable to develop under the normal circumstances (orphan drug), and
- The Committee on the Herbal Medicinal Products (HMPC), which assists the harmonisation of the procedures, and provisions concerning the herbal medicinal products in the EU Member States. Further it is responsible for

integrating the herbal medicinal products in the European regulatory framework.

For the products eligible for or requiring the central approval, a pharmaceutical company submits an application for a marketing authorisation to the EMEA. A single evaluation is carried out through the CHMP or CVMP. After proving the received documents for the quality, safety, and efficacy of the medicinal product the responsible committee should give a positive opinion. This opinion will be sent to the European Commission for transforming into a marketing authorisation valid for the whole of the EU.

6.2. Food and Drug Administration (FDA)

The FDA is an agency of the United States Department of the Health and Human Services. It is responsible for regulating the biologic products, blood products, cosmetics, dietary supplements, drugs (animal and human), foods (animal and human), medical devices, and radiation emitting devices in the United State. After proving the submitted documents for the quality, safety, and efficacy the FDA will approve or reject the drugs that the pharmaceutical companies want to market. Further, it verifies the safety, quality, efficacy, along with the drug interactions, and how the various drugs may work depending on age, race, and sex. To avoid the mistakes, the FDA ensures that the newly approved drugs have passed the vigorous testing, which includes the animal testing, clinical trials of the healthy individuals, and the clinical trials of the individuals suffering from the disease the drug is meant to treat.

6.3. National Agency for Medicines in European Countries

The National Agency for Medicines has to be notified of the clinical trials on the medicinal products that intervene with the inviolability of the trial subject

in order to investigate the effects or properties of a medicinal product, regardless of whether the investigational medicinal product has a marketing authorization. The National Agency for Medicine has to be informed about all clinical investigations.

7. Study Related Documents

There are a lot of the study related documents that has to be prepared before asking the EC/IRB and competent authority for their positive opinion. Further documents will be needed in the case of the changes after approval of the competent authority and EC/IRB.

- The investigators brochure
- The study protocol
- The protocol amendment
- The final study report
- The informed consent
- The trial file
- The Trial Master File (TMF)

7.1. Investigator's Brochure (IB)

The IB is a compilation of the clinical and non-clinical data on the investigational product(s). A medically qualified person generally participates in the editing of an IB, but the contents of the IB have to be approved by the disciplines that generated the described data. The IB will provide the investigators and others involved in the trial with the information to facilitate their understanding with many key features of the protocol, such as:

- The dose,
- The dose frequency/interval,
- The methods of administration, and
- The safety monitoring procedures.

The IB provides insight to support the clinical management of the study subjects during the course of the clinical trial. The IB will be reviewed at least

annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision is appropriate depending on the stage of the development and the generation of the relevant new information. However, in accordance with the ICH-GCP, all relevant new information has to be communicated to the investigators, to the EC/IRB, and regulatory authorities before it is included in a revised IB. The IB should include:

- A title page,
- A confidentiality statement,
- A table of contents,
- A summary,
- An introduction,
- The physical, chemical, and pharmaceutical properties and formulation of the substance,
- The non-clinical studies,
- The effects in the human, and
- The references.

7.2. Study Protocol

The study protocol has to be dated and signed by the sponsor, the principal investigator, and other involved principal investigators at the sites. It is a document which describes:

- The objective(s),
- The design,
- The methodology,
- The trial subjects,
- The schedule of tests, procedures, medications, and dosages,
- The length of the study,

- The statistical considerations, and
- The organization of a clinical trial.

The study protocol usually gives the background and rationale for the trial. It contains a study plan on which all clinical trials are based. The plan is designed to safeguard the health of the participants as well as to answer the specific research questions. The last version has to include all currently authorised amendments and a definition of the end of the trial. The study protocol must include at least the following information:

- The title page: the full name of the clinical trial, the abbreviated name of the trial, the sponsor's protocol number, the version number, the date of the protocol, the names of the sponsor, and the EudraCT number,
- The trial indication,
- The research method (controlled, uncontrolled), the structure of the trial (parallel groups, cross-over), randomisation (the method and procedure), and blinding (double blind, single blind),
- A list of the trial sites, and investigators,
- A summary of the protocol in the national language,
- A table of contents,
- The scientific rationale,
- The current knowledge,
- A description of the trial subjects,
- The inclusion and exclusion criteria,
- The estimated number of the subjects to be included in the trial,
- The timetable of the trial,
- The length of the treatment period,
- The follow up period,
- The treatment after completed the trial,

- The method of the administration, dose and dosing schedule of the investigational medicinal product and the comparator,
- The control groups and control treatment (placebo, other treatment, etc.),
- The criteria for dose reduction, and interruption,
- The criteria for suspending of the treatment,
- The allowed concomitant treatments,
- The forbidden concomitant treatments,
- The assessment of the efficacy,
- The assessment methods, and schedule,
- The assessment of the trial safety and related laboratory and other tests,
- The reporting of the adverse events reactions, and any systematic follow-up
- The precautions for the emergencies,
- The criteria for opening the trial code if applicable,
- Any adverse effects in the patient's relatives, nursing staff and the surroundings which may be caused by the investigational medicinal product and by the trial, and measures to prevent them,
- The processing, and recording of the data from the subjects participating in a trial,
- The information on the quality assurance methods,
- The measures used to ensure the authenticity of the collected data and the observance of the GCP,
- The statistical analysis methods, and results,
- The method for obtaining the informed consent of the trial subjects,
- The ethical aspects relating to the trial,
- The references, and
- The appendices to the protocol.

In the design of the Phase-Ia clinical trials the protocol has to describe the strategy for the managing the risks including a plan for monitoring the safety and managing of any adverse reactions, and the use of an independent safety monitoring board. When the design of the Phase-Ia studies include that the subjects receive a placebo it is important to take any decisions with respect to the subsequent dosing at the same dose level and or dose escalation, take into account the number of the subjects that might have received the active medicinal product. While one of the main purposes of a first-in-man trial is to assess tolerance the paramount factors have always to be:

- The safety,
- The rights and well-being of the volunteers,
- The choice of the subjects (patients or healthy individuals), and
- The value of what can be learned from the clinical trial.

7.3. Amendment

After the approval of the study protocol all changes in this protocol will be called the amendment. The competent authority and the EC/IRB have to be informed about all substantial amendments to the protocol. Also the sponsor is obliged to submit all relevant documents in support of such amendments to the competent authority, and the EC/IRB. The sponsor has to implement such amendments after it has received a favourable opinion of the EC/IRB, unless the changes consist of the urgent safety measures to protect the trial subjects. In the case the urgent measures are taken, the sponsor should inform the competent authority as soon as possible of the new event, the measures taken and any plan for further action. The following points must be considered by the amendments:

- The submission at the same time to both the EC/IRB and the competent authority,
- The identifiable (the sponsor's amendment code number, version, date, and changes) and signed by the sponsor or the authorised representative of the sponsor and the principal investigator in a multi-centre trials,
- The reasons for the amendment,
- The submission of all updated documents e.g.
  - Any new version of the investigator's Brochure (and/or Summary of Product Characteristics),
  - A new risk benefit analysis, if applicable, and
- By the submission of only separate pages with the changes both the old and new text should be indicated.

An EC/IRB involved in the clinical trial has to give an opinion on a proposed substantial amendment within 35 days. The amendment may be implemented after 35 days from the receipt of a valid notification of an amendment if the competent authority has not raised grounds for the non-acceptance. In the case that the competent authority consults a group or committee the competent authority has to notify the sponsor of the duration of the extension.

7.3.1. Substantial Amendments

The substantial amendments to the conduct of the clinical trial may arise from the changes to the protocol or from new information relating to the scientific documents in support of the trial. The substantial amendments to the trial are regarded as significant where they have a significant impact on:

- The safety or physical or mental integrity of the subjects,
- The scientific value of the trial,
- The conduct or management of the trial, and

- The quality or safety of any investigational medicinal product used in the trial.

7.3.2. Non-substantial Amendments

The sponsor does not have to notify the non-substantial amendments to the documentation provided to the competent authority, and the EC/IRB. However, they should be recorded, and be available on request for the inspection at the trial site and/or the sponsors premises as appropriate.

7.3.3. Urgent Amendments

The urgent amendment means that a sponsor and investigator have to take appropriate urgent safety measures to protect the subjects against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects. These safety measures such as temporarily halting of the trial may be taken without the prior authorisation from the competent authority. The sponsor has to inform the competent authority, and the EC/IRB concerned of the new events, the measures taken and their plan for further action as soon as possible. This should be by the telephone in the first place followed by a written report. When the sponsor halts a clinical trial (stops recruitment of new subjects and/or interrupts the treatment of subjects already included in the trial), the competent authority, and the EC/IRB will be notified within 15 days. The sponsor may not recommence the trial until the EC/IRB has given a favourable opinion, and the competent authority has not raised grounds for the non-acceptance of the recommencement.

7.4. Final Study Report

Upon the completion of the clinical trial, the sponsor has to provide the competent authority, the EC/IRB, and the investigator/institution with a summary of the trial's outcome. The final clinical study report is a full report of an individual study of any therapeutic, prophylactic, or diagnostic agent conducted in the patients, or healthy individuals, in which the clinical, statistical description, presentation, and analyses are integrated into a single report. The report contains information related to:

- The test drug including the active control or comparators,
- The patient data listings,
- The statistical documentation,
- The statistical analyses, and
- The description.

The clinical study report has to be complete, free from ambiguity, well organised, and easy to review. It provides a clear explanation of how the critical design features of the study were chosen, and the clear explanation on the plan, methods, and conduction of the study. The report with its appendices should contain the individual patient data, including the demographic and baseline data, and the detail of the analytical methods. The structure of the final study report can be as below:

- The title page,
  - The protocol identification code,
  - The study title,
  - The indication studied,
  - The development phase of the study,
  - The study initiation date,

- The study termination date,
- The study completion date,
- The name of the sponsor,
- The name of the principal investigator,
- The date of the report,
- The synopsis,
- A table of the contents,
- The definition of the terms,
- The ethical issue of the study,
- The patient and informed consent process,
- The investigators and study administrative structure,
- The introduction,
- A brief statement placing the study in the context of the development of the test drug,
- The critical features of the study,
- The study objectives,
- The study design,
- The selection of the study population,
- The treatments,
- The efficacy and safety variables,
- The data quality assurance,
- The statistical consideration,
- The study population,
- The disposition of the study population,
- The protocol deviations,
- An efficacy evaluation,
- A safety evaluation,

- The discussion and overall conclusions,
- The reference lists, and
- The appendices.

7.5. Informed Consent

Informed consent is the information sheets about the clinical trial which has been given to the subject and/or the parent/legal representative by the investigators. It has to be kept short, clear, relevant, and understandable to a lay person. It has to contain at least three elements:

- The consent to participate in the trial,
- The consent to archive the coded information, and for its transmission outside the site, and
- The consent to make the confidential personal information available for the quality control and quality assurance by:
  - The relevant personal from the sponsor,
  - A nominated research organisation on behalf of the sponsor, and
  - Inspections by the competent authorities/institutions assigned this task.

Informed consent documents are necessarily written for the people who don't know anything about the trial or about the treatment. They are also simplified to make them understandable to the people with the marginal literacy. Each informed consent has to contain at least the following information:

- The title of the study with a statement, that the treatment involves the research,
- The description of the purposes of the study e.g.,
  - The evaluation of the safety,
  - The doses finding,
  - The effectiveness,

- The procedures relating solely to the research (e.g., randomization, placebo control, additional tests),
- The appropriate alternative procedures or courses of the treatment,
- The treatment after end of the trial,
- The expected duration of the subject's participation,
- An explanation of the procedures used in the trial,
- The expected benefits to the subject,
- The expected risks,
  - The risks of the procedures relating solely to the research,
  - The expected risks of the study treatment,
- The unexpected risks,
  - The risks of the procedures relating solely to the research,
  - The unexpected risks of the study treatment,
- The study drugs and comparator,
  - The cost,
  - The labelling,
  - The route,
- An explanation of whom to contact in the event of a research-related injury to the subject,
- A statement describing the extent, which subject's records will be maintained,
- A statement describing the monitoring of the personal, disease, and treatment data by the monitors, and the competent authorities,
- A statement describing that the subject name will not be given to the other persons outside the trial site,
- A statement that the collected data will be submitted outside the trial site only as blinded,

- A statement that the subject decline to participate or to discontinue the participation at any time without penalty or loss of the benefits, and
- The description of any compensation or medical treatments that will be provided if injury occurs.

Further to the above mentioned points the additional elements have to contain the informed consent:

- A statement that the particular treatment or procedure may cause the risks to the subjects which are currently unforeseeable,
- A statement that there may be the unforeseen risks to the embryo or fetus[21],
- A statement about the mutagenicity, and teratogenicity,
- A statement that the subject has to meet the measures to prevent the pregnancy while in the study,
- A statement that the subject's participation may be terminated by the investigator without regard to the subject's consent,
- A statement that the subjects may be withdrawn from the study if they do not follow the instructions given to them by the investigator,
- A statement about the consequences of a subject withdrawal from a research,
- A statement that the significant new findings during the clinical trial will be provided to the subject, and
- A statement about the approximate number of the subjects to participate in the trial.

[21] The fetus is a developing mammal. The fetal stage begins eight weeks after the fertilization. The fetus is sensitive to the damage from the environmental exposures, though the toxic exposures can often cause the physiological abnormalities or minor congenital malformation.

7.6. Trial File

The Trial File (Investigator File) is a file which contains all essential documents relating to a clinical trial, before the trial commences, and during the trial conduction. The Trial File contains the essential documents which individually and collectively permit the evaluation of the conduct of a trial, and the quality of the data produced. All these documents serve to demonstrate the compliance of the investigator, and the sponsor with the ICH-GCP guidelines, and with all applicable regulatory requirements. Due to the section 8 of the ICH-GCP the Trial File documents can be grouped in three sections:

- The documents generated before the clinical phase of the trial commences,
- The documents generated during the conduction of the trial, and
- The documents generated after the completion or termination of the trial.

Before the trial conducted the Trial File has to be established at the trial site. An initiation visit of the trial can only be done when the monitor reviewed with the investigator, and confirm that all necessary documents are in the appropriate files. A final close-out visit of a trial can only be done when the monitor has reviewed, and confirmed that all necessary documents are in the appropriate files.

- **Patients**
  - The inclusion and exclusion criteria
  - The patient informed consent
  - The start of treatment fax
  - The end of treatment fax
  - The patient screening log
  - The identifications list of the enrolled patients
  - The signed and dated informed consent for all patients

- **AE/SAE Handling**

- The SAE contact person
- The SAE reporting form
- The blank SAE reporting forms
- All SAE reporting form completed at the particular site
- A List of the Adverse Events (not mandatory)

- **Protocol Related Documents**

- The protocol synopsis
- The protocol / amendments / addenda / administrative amendments
- The protocol and amendment signature pages
- The sample of the EC/IRB-approved site-specific patient information leaflet and informed consent form
- The documentation regarding the protocol deviations

- **Investigator's Brochure**

- The investigator's brochure, updates, amendments & addenda (e.g. triple-yes-AE notifications)

- **Administrative Documents**

- The CV of investigator and other study personnel
- The investigator contract
- The confidentiality agreement
- The authorised personnel form (original)
- The insurance / indemnity certificate and insurance conditions (incl. up-dates)
- The correspondence (letters, faxes, emails) and telephone reports
- The Clinical Study Report

- **Regulatory Affairs**

- The EC/IRB
- The application letter incl. list of the submitted documents
- The list of EC/IRB members
- The EC/IRB-approval of the protocol, amendments and addenda
- The acknowledgements by the EC/IRB of e.g. the administrative amendments or safety information
- The annual report of the study progress
- The final report to the EC/IRB and authorities at the study termination
- The competent authority

- **Study Medication and Other Supplies**

- The documentation of the study medication preparation
- The documentation of the drug transport and storage conditions (e.g. temperature log) (originals)
- The drug accountability form
- The medication request fax
- The certificate of the analysis for the study medication (copy)
- The instructions for handling of the study medication and other supplies
- The confirmation of the receipt of the study medication and other supplies
- The medication returns form (copy)

- **Clinical Specimen Management**

- The instruction of the blood collection
- The freezer temperature log
- The shipment records of courier

- **Laboratory**

- The normal ranges (incl. updates)

- The certificate(s) / QC assessment schemes (incl. updates)

- **Monitoring Visits**
- The monitoring visit log (original)
- The initiation visit report (copy)
- The monitoring visit response letters

- **Case Report Forms**
- The separate case

- **Laws and Regulations**
- The applicable laws, directives & guidelines
- The Declaration of Helsinki
- The ICH-GCP

The Trial File must be maintained, and updated throughout the study. It has to be kept in a secure environment. This file has to be made available for the monitoring, sponsor's audit, and inspections by the competent authorities. During the close-out visit of a trial the monitor has to confirm that all regulatory, investigator, and sponsor documents are present, and held in the appropriate files. The Trial File has to be retained for 15 years.

7.7. Trial Master File

Due to the EU Directive 2001/20/EC the trial master file (TMF) shall consist of the essential documents, which enable both the conduct of a clinical trial, and the quality of the data produced. These documents show whether the investigator and the sponsor have complied with the principles and guidelines of the ICH-GCP and with the applicable requirement and, in particular, with the Annex I to the Directive 2001/83/EC. All these documents shall demonstrate the compliance of the investigator, sponsor and monitor with the

GCP. Due to the section 8 of the ICH-GCP the TMF documents can be grouped in three sections:

- The documents generated before the clinical phase of the trial commences,
- The documents generated during the conduction of the trial, and
- The documents generated after the completion or termination of the trial.

The TMF has to be maintained, and updated throughout the study. The essential documents have to be made available for the sponsor's audit and inspection by the competent authorities. A close-out of a trial can only be done when the responsible person has confirmed that all regulatory, investigator, and sponsor documents are present and held in the appropriate files. The TMF has to be retained for 15 years.

7.8. Case Report Form

A case report form (CRF) is a printed or electronic document which has been designed to record all available information on each trial subject required by the protocol. The CRF has to be completed by the study site so that they are accurate, complete, and legible. Any correction or change to a CRF has to be dated, initialled, and explained (if necessary) by the authorised personals. The original entries to the paper or printed CRF have not to be obscured by the correction fluid or erased. The following information and requirements are to be followed by completing a paper CRF:

- The use of a black ballpoint pen for the permanency,
- All entries has to be legible,
- On every page has to appear,
  - The protocol number,
  - The site identification number,
  - The subject identifier e.g. the subject initial and subject number,

- Do not erase or use the correction fluid,
- The corrections by,
  - The drawing a single horizontal line through the error,
  - The entering the correct data,
  - The initialling, and dating the change, and
- All data, dates should corroborate.

The data reported on the CRF that are derived from the source documents has to be consistent with the source documents (e.g. hospital records, lab notes, X-rays, photographic negatives, records kept in pharmacy). The discrepancies from these records have to be explained.

7.9. Source Documents

The source documents are the original records, and certified copies of the original records of the clinical findings, observations, or other activities in a clinical trial documented by the subjects, authorised personals, or other medical records. They are the original trial documents of the patient files governed by the relevant general provisions and regulations. The source documents are:

- The personal data
- The medical records, and
- The health records.

Also, the source documents contain the systematic information about the patient's medical history and care. There are many ethical and legal issues for providing these data to the third-party, the degree of the access, and the appropriate storage and disposal.

7.10. Personal Authorisation Form

The investigator has to complete a personnel authorization form in which the personnel at the investigational site will be allocated to the respective responsibilities.

7.11. Query

The Data Query Form (DQF) or Data Clarification Form (DCF) is a questionnaire which is specifically used in the clinical trial. The DCF/DQF is the primary form for the data clarification. This tool has been used by the trial sponsor or CRO towards the investigator to clarify the discrepancies during, and after the data collection. The investigator will response and clarify the discrepancies. It is an important part of the data validation process in the clinical trial.

7.12. Protocol Violation

A protocol violation is any action involving a research subject (or potential subject) which is outside the actions specified in the study protocol. For example while some patients may not have followed the protocol, either accidentally or deliberately (non-compliance) or their condition may have led to the clinician giving them an alternative treatment to the one they were originally allocated to. Protocol violations emerge when there is a variance in a research study between the protocol and the actual activities performed by the research team. These violations can occur as a result of the poor investigator training. Due to the FDA regulations all protocol deviations and/or instances of the non-compliance with the EC/IRB regulations has to be reported to the EC/IRB by the principal investigator as soon as the violations are discovered. When such instances are discovered, the EC/IRB has to act promptly and to

ensure the investigator action regarding compliance with the human subject protection requirements and, if necessary, to halt enrollment into a study. Also, the EC/IRB can sanction, suspend, or terminate approval if there are serious or continuing the investigator non-compliance with the policies, requirements or determinations of the IRB /EC.

The protocol violation can be divided in:

- The Minor Protocol Violations, and
- The Serious Protocol Violations.

7.12.1. Minor Protocol Violations

The Minor protocol violations are the non-compliance with the study protocol and regulatory guidelines that usually does not have:

- Any substantive effect on the safety or well-being of the trial participants,
- Caused any changes on the risk/benefit ratio,
- Affect the scientific analysis of the collected data,
- Resulted from willful or knowing misconduct on the part of the investigator(s), and
- Violate any basic ethical principles.

The common minor protocol violations include e.g.:

- The failure to perform the certain study-related tasks, and
- The failure to perform the follow-up visits according to the protocol.

7.12.2. Serious Protocol Violations

The serious protocol violations are the non-compliance with the study protocol and regulatory guidelines that usually have:

- A significant risk of the substantive harm to the trial participants,

- Caused the damage to the scientific integrity of the collected data,
- Resulted from the evidence of willful or knowing misconduct on the part of the investigator(s), and
- Ignored the established research, medical, and ethical principles.

Protocol Waiver Request Protocol Number ……..	
Principal investigator ……	Site number ……
Name of Requester …….	Date …….
For the following Inclusion/Exclusion criteria (Number …….) this waiver is requested. Due to the following arguments we request this protocol deviation: …… ……	
_____ Investigator / Responsible Signature	
Exemption granted: Yes ☐ No ☐ Approval/refusal information: …… …… _____ _____ Signature of Company Study Manager Date _____ Print Name	

The common serious protocol violations include e.g.:

- The enrolling a subject outside any of the inclusion/exclusion criteria,
- The use of an unapproved or expired informed consent document,
- The record keeping and documentation failures, and
- Incorrect study medication or dosing.

7.13. Waiver

The waiver is an exemption for the inclusion of a subject in the clinical trial. An example of a written waiver is when a sponsor of the clinical trial accepts that the investigator can include a subject who does not fulfil all the inclusion and exclusion criteria in the clinical trial he/she will give it as a waiver. The waiver will be given in the written form, and has to be documented.

8. Individual and Organisation Involved in Clinical Trials

Different organisation and persons are involved in performing the clinical trials successfully. On the one side there are the investigators, the clinical trial side, the sponsor, and on the other side the competent authority, and EC/IRB.

8.1. Investigator

There are different types of the investigators who are involved in performing the clinical trials. In every country there is one leading investigator and other investigators at different sides. The investigator can be a doctor or a person following a profession agreed in the Member States of EU for the investigations because of the scientific background and the experience in the patient care it requires. The principal Investigator is the lead scientist for conducting the clinical trial at a trial site. Other investigators at the same site are calling sub-investigators. The principal investigator is responsible:

- For ensuring that the trial is conducted according to,
  - The signed investigator statement,
  - The investigational plan, and
  - The applicable regulations,
- For protecting,
  - The rights,
  - The safety, and
  - The welfare of the subjects under the investigator's care, and
- For the control of the drugs under the investigation.

According to the ICH-GCP guideline (4.1.1) the investigators have to be qualified by the education, training, and experience to assume the responsibility for the proper conduct of the clinical trial. The investigators has

to meet all the qualifications specified by the applicable regulatory requirements, and has to provide the evidence of such qualifications through the up-to-date curriculum vitae and other relevant documentation requested by the sponsor, the EC/IRB, and the regulatory authority. Further, the investigator (4.1.2) has to be thoroughly familiar with the appropriate use of the investigational product(s), as described in the clinical study protocol, in the current Investigator's Brochure, in the product information, and in the other information sources provided by the sponsors.

The investigator (4.1.3) has to be aware of, and has to comply with the GCP and the applicable regulatory requirements. Further, the investigator/institution (4.1.4) has to permit the monitoring and auditing by the sponsor, and the inspection by the appropriate regulatory authorities. Also, the investigator (4.1.5) has to maintain a list of the appropriately qualified persons to whom the investigator has delegated the significant trial-related duties. Before commencing the clinical trial the investigator has to provide the sponsor with the following documents:

- The signed investigator protocol agreement,
- The signed investigator GCP knowledge,
- The investigator statement (FDA Form 1572; 21 CFR 312.53),
- The CV of all involved site personals,
- The financial disclosure form,
- The clinical trial site qualification form,
- The signed clinical trial agreement, and
- The delegation authority form.

8.1.1. Control of Investigational Drug Handling

The investigator has to ensure that the investigational drug will be administered only to the subjects who are authorized to receive it. Also the investigational drug has to be administered to the subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.

- Recordkeeping for the disposition of the drug. Adequate records of the disposition of the drug, including the dates, quantity, and use by the subjects has to be maintained by the investigator. On the end of the investigation the investigator has to return the unused supplies of the drug to the sponsor.
- Trial Subject histories. Accurate case histories that record all observations and other data to the investigation on each individual administered the investigational drug or employed as a control in the investigation has to be maintained by the investigator. In the case history for each individual the investigator has to document that the informed consent was obtained prior to the participation in the study.

8.1.2. Assurance of EC/IRB Review

Before starting a clinical trial the investigator has to assure that an EC/IRB that is responsible for him, and continuing the review of the trial, has approved the proposed clinical study.

8.1.3. Inspection of Clinical Trial Sites

An investigator has upon the request from any properly authorized persons of the involved competent authorities (e.g. EMEA, FDA), at reasonable times, to permit such persons to have access, copy, and verify any records or reports made, and used by the investigator.

8.1.4. Disqualification of Investigator

An investigator involved in a clinical trial can be disqualified by the EC/IRB, the sponsor, or the competent authority when there are information indicating that an investigator has submitted to the competent authority (e.g. EMEA, FDA), the EC/IRB, or to the sponsor false information in any required reports. In these cases the investigator shall have an opportunity to explain the matter in the writing form.

8.2. Sponsor

The sponsor is an individual, company, institution or organisation, which takes the responsibility:

- For the initiation,
- For the management, and
- For the financing of a clinical trial.

The sponsor is able to use a clinical research organisation (CRO) or other body to carry out the trial-related activities on their behalf.

8.2.1. Investigator Reports

The sponsor has to provide the competent authorities and the EC/IRB with the reports about the progress of the clinical trial. Also, the sponsor has to submit the annual reports on the progress of the clinical investigations. Further, the sponsor has to provide the investigators, the EC/IRB, and the competent authorities with the safety reports which have been generated by the sponsor from the adverse effects that may reasonably be regarded as caused by, or probably caused by the drug. On the end of the clinical trial the sponsor has to

provide the investigators, the EC/IRB, and the competent authorities the final study report.

8.2.2. Assurance of EC/IRB Review

Before commencing a clinical trial the sponsor has to assure that an EC/IRB that is responsible for the involved trial sites, and continuing the review of the trial, has approved the proposed clinical study. The sponsor has also to assure that he will promptly report to the EC/IRB all changes in the research activity, and all unanticipated problems involving the risk to the subjects or others, and that he will not make any changes in the research without the EC/IRB approval, except where necessary to eliminate the apparent immediate hazards to the subjects.

8.2.3. Outsourcing in Clinical Trial

Due to the downsizing strategies the pharmaceutical industry has been concentrating the resources on the core skills, and outsourcing[22] some activities. The contract research organisations (CRO) will become more and more important strategic partners for the pharmaceutical companies by this process. Outsourcing offers a number of the advantages to the sponsor e.g.:

- The converting the fixed costs of maintaining the personnel, expertise, and facilities necessary for the management of the clinical trials into the variable costs,
- The increased complexity of the clinical trials,
- The increased amount of the data required from the clinical trials,

[22] The outsourcing means converting the fixed costs of maintaining the necessary personnel, infrastructure and expertise into the variable costs of paying a sub-contractor to perform that process when it is required. Also, it gives the companies the flexibility to acquire skills, and technologies in a cost, and time efficient way. Outsourcing some activities avoid get heavy financial backing to develop them in house.

- The knowledge of the regulatory affairs in a particular country of interest,
- The multinational nature of the clinical trials,
- The Reduction of the required time to develop a new drug, and
- The requirement of the large participants.

8.2.4. Legal representative

The 5th recital to the EU Directive 2001/20/EC states that "*the notion of legal representative refers back to national law and consequently may include natural or legal persons, an authority and/or a body provided for by natural law*". It would be for the sponsor to nominate the representative and the representative to indicate their acceptance. In the terms of the establishment, the minimum requirement would be to have their registered office, the central administration or the principal place of the business within the community. The sponsor would retain the overall liability for the compliance with the regulations but he/she might ask the legal representative to act as his or her agent in relation to the certain matters. This would presumably be dealt with in any formal agreement between the two. Due to the EU Directive 2001/20/EC if a sponsor delegates any or all of his trial-related functions to an individual, a company, an institution or an organisation the sponsor remains responsible for ensuring that the conduct of the trials, and the final data generated by those trials comply with this directive.

8.2.5. Sponsor Responsibility

The sponsor of a clinical trail is responsible to ensure that all involved individuals know and work in the accordance to the ICH-GCP. Also, the competent authorities have to be notified whenever the sponsor becomes aware of the serious breaches of the ICH-GCP, for example:

- When the investigators or team members at a site put the trial subjects safety at risk,
- When the investigators or team members persistently fail to comply with the study protocol or the ICH-GCP, or
- When the investigators or team members falsify the data.

8.3. Trial site

The trial site is a medical facility with the qualified personals for performing the clinical trial. For fulfilling their responsibilities the trial site has to have the adequate resources e.g. space, and personal.

Some trials have to take place in the clinical facilities by the medical staff with an appropriate level of the training and expertise, and an understanding of the investigational medicinal product, its target and mechanism of action. In the Phase-Ia trials the immediate access to the facilities for the treatment of the medical emergencies is necessary. These facilities have to have the adequate capacity for stabilising the individuals in an acute emergency, and ready availability of the Intensive Care Unit facilities.

8.4. Trial Subjects

The trial subjects can be divided in the healthy volunteers, or patients with one special diagnosis. Further, in the case of the investigation with the drugs for the treatment of the HIV, Cancer, Parkinson, Alzheimer disease, and coronary heart disease only the patients with the same disease can participate in the trial. It is common for the healthy subjects to be paid for their participation in the research, especially in the early phases of the investigational drug, biologic or device development. The payment to the research subjects for the participation in the clinical trials is not considered a benefit, it is a recruitment

incentive. The amount and schedule of all payments will be presented to the EC/IRB at the time of the initial review.

For the clinical trials with the high-risk medicinal products in a Phase-Ia the choice of the subjects, i.e. the healthy subjects or patients, has to be fully justified by the Sponsor on a case-by-case basis. Several factors have to be considered:

- The presence of the target in the healthy subjects or in patients,
- The possible higher variability in the patients,
- The risks inherent in the type of the medicinal product,
- The molecular target of the medicinal product, and
- Immediate and potential long term toxicity.

8.5. Contract Research Organization

A CRO offers the sponsor of the clinical trial a wide range of the pharmaceutical research services. The CRO is an independent contractor with the sponsor, one or more of the obligations of a sponsor e.g. the design of a protocol, the selection of the trial sites, the monitoring of the trial sites, the evaluation of the reports, and the preparation of the documents to be submitted to the competent authorities (e.g. EMEA, FDA). The CRO can offer the following services:

- The central laboratory services for processing the trial samples,
- The monitoring of the clinical trial,
- The clinical trial management,
- The data management,
- The preparation of the documents for the submission to e.g. the EMEA, FDA, and
- The product development and formulation.

8.6. Clinical Research Associate

A clinical research associate (CRA) may function as a monitor of the clinical trials. The CRA works directly with the sponsor of a clinical trial, as an independent freelancer, or for a CRO. As a monitor ensures the CRA the compliance with the clinical trial protocol, checks the clinical site activities, makes on the site visits, reviews the CRF, and communicates with the clinical investigators. Most CRA were trained as nurses, but the nutritionist, musicians, pharmacist, engineers, statisticians, biologists, epidemiologists, microbiologists, and computer scientists have all become successful and effective monitors. The monitors have to be knowledgeable about their company's SOP's and work in conformity with them. They have to take part in the ongoing training activities to keep their knowledge up-to-date. The most important quality for a monitor is a commitment to accuracy, completeness, and logic. The CRA needs to have a good knowledge of the ICH-GCP, and local regulations.

8.7. DSMB

The knowledge and experience that are generated during the process of the research can raise the important practical, scientific, and ethical issues. The emerging data can affect the acceptability of continuing a trial, either because one study arm is shown to be superior to another or because a study arm is causing the unanticipated harm. On the other hand the isolated experience whether good or bad, within the trials can be misleading to those involved with the research and if acted upon can undermine the integrity of the trial. To address some of these issues and to consider the relevance of the results obtained from the other research, many trials use an independent Data Safety

Monitoring Board (DSMB) to evaluate the emerging data from the clinical trials. The DSMB is an independent group of the experts who monitor the patient safety and treatment efficacy data during a clinical trial. While many randomized clinical trials are double blind the persons (e.g. doctors, subjects, and sponsors personals) involved with the trial do not know what treatment was given to the trial subjects. In this case only after the trial database is finalized the blinded code will be broken and the true treatment assignments will be disclosed.

The DSMB is a group (typically 3 to 7 members) who are independent of the company sponsoring the clinical trial. At least one DSMB member will be a statistician. The clinicians knowledgeable about the disease indication should be represented, as well as the clinicians knowledgeable in the fields of any major suspected safety effects. The DSMB will convene at the predetermined intervals (three to six months typically) and review the un-blinded results, i.e. the results split by the experimental and control arms. After reviewing the un-blinded data the DSMB has the power to recommend the termination of the trial based on the evaluation of these results. There are typically three reasons a DSMB might recommend the termination of the trial:

- Safety concerns. If the adverse events of a particularly serious type are more common in the experimental arm compared to the control arm the DSMB strongly consider the termination of the trial. This evaluation has to be made in the consideration of the risk/benefit ratio.
- Outstanding benefit. If the experimental arm is shown to be undeniably superior to the control arm the DSMB may recommend the termination of the trial. This would allow the company sponsoring the trial to get the regulatory approval earlier and to allow the superior treatment to get to the patient population earlier.

- Futility can be the most common reason to stop a clinical trial. It is the case when the experimental arm and the control arm have nearly the identical results.

8.7.1. Mandate of DSMB

The protection of the patient safety is the primary mandate of the DSMB. If the serious adverse events of a particular type are more common in the experimental arm compared to the control arm, the DSMB would strongly consider the termination of the trial. This evaluation will be made by the consideration of the risk/benefit quotient.

8.8. Inspectors (Auditors)

The inspectors or auditors are persons, who audit the clinical trial, the EC/IRB or the sponsors as representative of the sponsor or the competent authorities. They shall have education at the university level, or the equivalent experience, in the medicine, pharmacy, pharmacology, toxicology or other relevant fields. Also, the inspectors have to full fill the following requirements:

- To have the appropriate training,
- To be trained regularly after the assessment of their training needs,
- To take the appropriate action for the maintaining and improving their skills,
- To have the knowledge of the principles and processes that apply to the development of the medicinal products and clinical research,
- To have the knowledge of the applicable community and national legislation and guidelines applicable to the conduct of the clinical trials and the granting of the marketing authorisations,

- To be familiar with the procedures and systems for the recording the clinical data, and
- To be familiar with the organisation and regulation of the healthcare system, where appropriate, in third countries.

The EU Member States have to maintain the up-to-date records of the qualifications, training and experience of each inspector. She/he has to be provided with a document setting out the SOP and giving the details of the duties, responsibilities and ongoing training requirements. Further, each inspector has to sign a statement declaring any financial or other links to the parties to be inspected.

9. Informed consent Process

At the Nuremberg trials[23] the doctors and public health officials involved in the horrible crimes attempted to excuse themselves by the arguing that there were no explicit rules governing the medical research on the human beings in Germany during the period and that research practices. In this context the Nuremberg code of 1947 is generally regarded as the first document to set out the ethical regulations in the human experimentation based on the informed consent.

The introduction of the scientific and experimental methodology into the clinical medicine in the nineteenth century brought with it an increased demand for the experimentation on the human subjects. This research was done mainly on the patients in the hospital, often without their consent. As formulated in the Nuremberg code, a careful cost-benefit calculation and a detailed research plan with the animal experimentation beforehand are already required to minimise the risk to the human subjects. The publication of the results of the new therapy must respect the patient's dignity and the mandate of the humanity.

Informed consent is a process of the information in addition to reading and signing the informed consent document, the subject recruitment materials, the verbal instructions, the question/answer sessions, and the measures of the subject understanding. According to the Article 5 of the biomedicine convention[24]: "An intervention in the health field has only to be carried out

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[23] The Nürenberg Trials are a series of the trials most notable for the prosecution of the prominent members of the political, military and economic leadership of the Nazi Germany. From 1945 to 1949 the trials had been hold in city Nürenberg.

[24] The convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of the Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo, 4.IV. 1997

after the person concerned has given free the informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw her/his consent at any time."

The EC/IRB, competent authority, clinical investigators, and sponsors all share the responsibility for ensuring that the informed consent process is adequate. The informed consent document has to be the basis for a meaningful exchange of the information between the investigator, and the trial subject. The clinical investigator is responsible for ensuring that the informed consent is obtained from each trial subject before his/her participation in the clinical trial.

The trial subject/representative has to sign the consent form, and enter the date of signature on the consent form to permit the verification that the consent was actually obtained before the subject underlay the trial related procedures. If the consent is obtained on the same day that the subject's participation in the study begins, the investigator has to document that the consent was obtained prior to the participation in the trial related procedures. A copy of the consent document has to be provided to the trial subject, and the original signed consent document has to be kept in the study records[25].

- The consent process begins when a potential trial subject is initially contacted by the investigator for the participation on the trial.
- The recruitment of the subjects for the participation in a clinical trial after the approval of the study by EC/IRB.
- The information materials given to the potential trial subject and/or the parent/legal representative has to be kept:
  - Short,

[25] Due to the FDA regulations the subject's copy does not require to be a signed copy, although a photocopy with signature(s) is preferred.

- Clear,
- Relevant,
- Understandable to a lay person, and
- In a language the subjects knows.

➢ In the cases where the minors or incapacitated subjects are to be included, the subject should be given the information according to his/her capacity to understand. This should include a statement that the subject's decision not to participate or to withdraw from a trial will be respected, even if the consent is given by parent/legal representative.

➢ The subject has to be informed of the possibility to withdraw the consent without giving any reason.

➢ The subject has to be informed that all previously collected identifiable samples will be destroyed to prevent the further analyses.

➢ After withdrawal of the consent no new information will be collected from the subject and added to the existing data or a database.

➢ The trial subject has to consent to the scrutiny of the personal information during the inspection by the competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available.

9.1. Basic Elements of Informed Consent

During the informed consent process the following information has to be provided to each trial subject:

➢ The clear information that the treatment involves research,

➢ An explanation of the purposes of the research,

➢ The clear description of any study procedures which are experimental,

- For the studies of the investigational articles a statement that a purpose of the study includes an evaluation of the safety of the test article,
- For the studies that evaluate the effectiveness of the test article a statement that a purpose of the study includes an evaluation of the effectiveness,
- A description of any reasonably foreseeable risks or discomforts to the trial subject,
- A description of the trial related procedures,
- An explanation of the risks of the procedures or tests relating solely to the research,
- A description of any anticipated benefits to the subject,
- A disclosure of the appropriate alternative procedures or courses of the treatment,
- A statement describing the extent of the records identifying the subject,
- A Statement that the competent authorities may inspect the study and medical records,
- A statement that the sponsor personal (Monitor, Auditor) check the study and medical records,
- An explanation of any compensation that subject will receive during the trial,
- An explanation of any medical treatments which are available if the injury occurs,
- An explanation of any compensation available in the case of the injury,
- An explanation of whom to contact for the answers to the pertinent questions about the research and research subjects' rights,
- A statement that the participation is voluntary,
- A statement that refusal to participate will involve no penalty or loss of the benefits,

- A statement that the trial subject may discontinue the participation at any time without penalty or loss of the benefits,
- A statement that the particular treatment or procedure may involve the risks to the subject which are currently unforeseeable,
- A statement that the particular treatment or procedure may have the unforeseen risks to the embryo or fetus ,
- A statement about the preclinical teratology and reproductive toxicology studies. When these studies are not completed prior to the initial studies in the humans, the male and female study subjects has to be informed about the lack of the full characterization of the test article and the potential effects of the test agent on the conception and fetal development,
- A statement that the subject's participation may be terminated by the investigator without regard to the subject's consent,
  - When the subject does not "follow the study procedures",
  - When there is not any further benefit for the subject,
  - When there is a risk for the subject health,
- Any additional costs to the subject that may result from the participation in the research,
- A statement that the new significant findings developed during the course of the research will be provided to the subject,
- The expected duration of the trial for the subject, and
- The approximate number of the subjects involved in the study.

Study Title ……..

Investigator Name _____

Investigator Address _____

Contact Phone _____

Dear Patient

You are being invited to take part in a research study, also known as a clinical trial. The main objective of this document is to provide the potential study participant with the information necessary to help in deciding to participate in this trial. The document is intended to provide a full but simple understanding of the scientific reasons for the investigation. This document also informs you about your rights and responsibilities in participating in the trial.

Your physician has explained you that …… has been diagnosed.

Study treatment

Other treatment options

Outside this clinical study, many hospitals will treat patients with similar manifestations with ……

Voluntary participation

Your participation in this trial is entirely voluntary. You can decide to withdraw your consent from participation the trial at any time without giving any reason and without any negative consequences for your further treatment.

Financial aspect

Insurance

Sponsor has a special insurance (Public and Products Liability Insurance) covering claims caused by the study treatment and not covered by the malpractice insurance of the respective hospitals. Such claims will have to be announced to the local study investigator who will then inform the sponsor.

Assurances

- My participation is voluntary and I am free to withdraw from the clinical research study at anytime without prejudice to my future care. If I decide to withdraw, I should notify my doctor so that my part in the study may be stopped in an orderly manner and my future care can be discussed.
- I or my legally acceptable representative will be kept informed, in a timely manner, of any information that may relate to my willingness to continue participation in the study. At the discretion of my doctor(s) and sponsor, I or my legally acceptable representative may be asked to sign a revised

informed consent or consent addendum that provides this information.

- I agree that sponsor can use my medical data for the development of commercial pharmaceutical products. Sponsor and other researchers may use these data and may patent or commercialize discoveries or inventions that result from this research. Neither sponsor nor other participants in this research will compensate me if this happens.
- I can ask questions at any time about this study. If I feel that I have experienced an adverse reaction to the research drug(s) or procedures, or if I feel unusually unwell during the study, I should contact Dr._____ at _____
- In signing this document, I confirm that I agree to be part of this study and that I have received my own copy of this document.

Signatures

_____	_____	_____
Subject Name	Place and Date	Signature
_____	_____	_____
Investigator Name	Place and Date	Signature

9.2. Legal Representative

The *"Legal representative"* is only defined as a person, which relates to a legal representative for the incapacitated adults or minors in the context of the consent. The 5th recital to the Directive 2001/20/EC states that "the notion of legal representative refers back to national law and consequently may include natural or legal persons, an authority and/or a body provided for by natural law".

9.3. Clinical Trials on Minors

A clinical trial on the minors can be performed only after:

- The informed consent of the parents or legal representative has been obtained,
- The consent must represent the minor's presumed will,

- The minor has received the informed consent document according to its capacity of understanding,
- To accept the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse the participation or to be withdrawn from the clinical trial at any time,
- Some direct benefit for this group of the patients will be obtained from the clinical trial
- No incentives or financial inducements are given except the compensation,
- Such research has either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors
- The clinical trials have been designed to minimise
  - The pain,
  - The discomfort,
  - The fear, and
  - Any other foreseeable risk in relation to the disease and developmental stage,
- The involved EC/IRB which has endorsed the protocol, has the paediatric expertise, and
- The interests of the trial subject always prevail over the other interests.

9.4. Incapacitated Adults

In the case of the incapacitated adults incapable of giving the informed legal consent, all relevant requirements listed for the persons capable of giving such consent shall apply. The inclusion of the incapacitated adults in the clinical trial is allowed only if:

- The informed consent of the legal representative has been obtained,

- The informed consent has to represent the subject's presumed will,
- The informed consent may be revoked at any time, without detriment to the subject,
- The incapacitated adults has received the informed consent document according to its capacity of understanding regarding the trial, risks and benefits,
- The explicit wish of a subject who is capable of the forming an opinion and the assessing this information to refuse the participation in, or to be withdrawn from, the clinical trial at any time,
- To accept the explicit wish of an incapacitated adults who is capable of the forming an opinion and the assessing this information to refuse the participation or to be withdrawn from the clinical trial at any time,
- No incentives or financial inducements are given except the compensation,
- Such research has either relate directly to a clinical condition from which the incapacitated adults concerned suffers or be of such a nature that it can only be carried out on such incapacitated adults,
- The clinical trials have been designed to minimise
  - The pain,
  - The discomfort,
  - The fear, and
  - Any other foreseeable risk in relation to the disease and developmental stage,
- The risk threshold and the degree of the distress shall be specially defined and constantly monitored,
- The involved EC/IRB which has endorsed the protocol, has the expertise in the relevant disease and the patient population concerned,
- The interests of the trial subject always prevail over the other interests, and

- The expectation that the administration of the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

- According to the Article 17 of the biomedicine convention: Research on a person without the capacity to consent as stipulated in the Article 5 may be undertaken only if all the following conditions are met:
- The conditions laid down in the Article 16[26], sub-paragraphs i to iv, are fulfilled,
- The necessary authorisation provided for under the Article 6[27] has been given specifically and in writing,
- The research of the comparable effectiveness cannot be carried out on the individuals capable of giving the consent,
- The person concerned does not object, and

[26]The Protection of the persons undergoing the research: Research on a person may only be undertaken if all the following conditions are met: there is no alternative of comparable effectiveness to research on humans; the risks which may be incurred by that person are not disproportionate to the potential benefits of the research; the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of the research, and multidisciplinary review of its ethical acceptability; the persons undergoing research have been informed of their rights and the safeguards prescribed by law for their protection; the necessary consent as provided for under Article 5 has been given expressly, specifically and is documented. Such consent may be freely withdrawn at any time.

[27]Protection of persons not able to consent: Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit. Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity. Where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The individual concerned shall as far as possible take part in the authorisation procedure. The representative, the authority, the person or the body mentioned in paragraphs 2 and 3 above shall be given, under the same conditions, the information referred to in Article 5. The authorisation referred to in paragraphs 2 and 3 above may be withdrawn at any time in the best interests of the person concerned.

- The results of the research have the potential to produce the real and direct benefit to his or her health.

Exceptionally and under the protective conditions prescribed by the law, where the research has not the potential to produce the results of the direct benefit to the health of the person concerned, such research may be authorised the subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions:

- The research has the aim of contributing, through the significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of the results capable of the conferring benefit to the person concerned or to the other persons in the same age category or afflicted with the same disease or disorder or having the same condition, and
- The research entails only minimal risk and minimal burden for the individual concerned.

9.5. Informed Consent Responsibility

The principal investigator or a sub-investigator has fully to inform the trial subject of all pertinent aspects of the clinical trial. The subject has to receive the written information, which has the favourable opinion by the EC/IRB.

Prior to a patient's participation in the clinical trial, the written informed consent form has to be signed and dated by the trial subjects or by the subject's legally acceptable representative. Further, the informed consent has to be signed by the investigator who conducted the informed consent discussion.

9.6. Payments

It is common for the healthy subjects to be paid for their participation on the research trials, especially in the early phases of the investigational drug, biologic or device development. The payment to the trial subjects for their participation in the trials is not considered a benefit. It is only a recruitment incentive. The amount and schedule of all payments will be presented to the EC/IRB at the time of the initial review. The EC/IRB has to review both the amount and method of the payment to the trial subjects to assure that neither the present problems of the coercion or undue influence on the trial subjects. The EC/IRB should determine that the amount paid as a bonus for the completion is reasonable and not so large as to unduly induce the subjects to stay in the study when they would otherwise have withdrawn. All information concerning the payment, including the amount and schedule of the payment(s), should be set forth in the informed consent document. According to the ICH-GCP the EC/IRB should ensure that the information regarding the payment to the subjects, including the methods, amounts, and schedule of the payment to the trial subjects, is set forth in the written informed consent form and any other written information to be provided to the trial subjects. Further, the way payment will be prorated should be specified.

The payment to the subjects who withdraw from the trial may be made at the time they would have completed the trial.

9.7. Amended Informed Consent From

In the different cases e.g. the adverse events, and the amended study protocol there is a need for the amended informed consent form which will be discussed with the subjects who are ongoing in the clinical trials.

The ongoing trial subjects have to be informed only about the new knowledge or changes which occurred during the trial. In these cases the subject will not understand why they have to sign a new complete informed consent form. Also, there is the necessity to concept two different informed consent forms:

1. Informed consent form which contain the changes for the ongoing subjects, and
2. Informed consent form for the new subjects.

9.8. Documentation of Informed Consent

Informed consent has to be documented by the use of a written consent form approved by the EC/IRB. It has to be signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

In the hospital charge investigator shall document that the patient has been informed and signed the informed consent form.

The treatment and procedures for the clinical trial (……..) has been discussed with the patient (Name and birthdate) on …… by Dr……. The subject has given her/his written consent on …….. After approving all inclusion and exclusion criteria the patient has been registered (randomized) in the clinical trial on …… with the study number……. The sponsor of the trial is ……..

---------- ----------

Date Investigator / Study coordinator

9.9. Post-randomized Consent

The post-randomized consent is known as the “Zelen's design”. In this design, the subjects will be randomized to either the treatment group or the control group before being consented. Because we know which group a given patient is assigned to, those subjects receiving standard care does not need to be

consented for the participation in the study. Also, consent will only be needed for the privacy issues. On the other hand those subjects randomized to the experimental group will be consented as usual.

9.10. Informed Consent in Emergency

When, because of an emergency situation, the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned.

- The intervention shall be carried out for the direct health benefit of the patient, and
- The intervention in question shall be medically necessary and unable to be delayed.

For an emergency use of the unapproved drugs, the physician require to obtain the informed consent of the subject or the subject's legally authorized representative certify in writing all of the following points that:

- The subject is in a life-threatening situation where the use of the test article is necessary,
- The informed consent cannot be obtained because of an inability to communicate with the subject,
- There is no sufficient time to obtain the consent from the subject or subject's legal representative, and
- There is no other alternative method of the approved or generally recognized therapy which provides an equal or greater likelihood of saving the subject's life.

The Declaration of Helsinki states that “Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should

be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population."

After the subjects recovery or as soon as possible the informed consent for the continued participation in the trial has to be obtained from either the patient or the legally authorised representative. According to the Article 8 of the biomedicine convention: Emergency situation has been defined as "when because of an emergency situation the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned."

9.11. Methods for Recruiting Study Subjects

The methods and material that the investigators propose to use to recruit the subjects has to be reviewed by the EC/IRB. There is no necessity for the EC/IRB review and approve listings of the clinical trials on the internet, because these listings do not provide additional safeguard and is not required when the system format limits the information provided to the basic trial information, such as:

- The title
- The purpose of the study
- The protocol summary
- The basic eligibility criteria,
- The study site location(s), and
- The contact for the further information.

Advertisement to recruit the subjects has to be limited to the information the prospective subjects need to determine their eligibility and interest. The FDA considers the direct advertising for the study subjects to be the start of the

informed consent and the subject selection process. The EC/IRB has to review and approve the direct advertising as part of the package for the initial review. Also, the EC/IRB review of the advertising concepts will assure that it is not unduly coercive. The EC/IRB has to receive and review:

- The information contained in the advertisement
- The mode of its communication,
- To determine that the procedure for the recruiting subjects is not coercive,
- To determine that the procedure for the recruiting subjects does not state or imply a certainty of the favourable outcome or other benefits,
- The final copy of the printed advertisements,
- The relative size of the type used, and
- The other visual effects.

The advertisement shall not to contain any claim:

- That the drug, or biologic is safe or effective for the purposes under the investigation,
- That the test article is known to be equivalent or superior to any other drug, or biologic,
- That the subject will "receive new treatments", and
- That the subject will be paid.

9.12. Screening Period Prior to Study Enrolment

Before the screening tests have been performed an investigator has to discuss the possibility of the entry into a study with a prospective subject. Also, when the screening tests have to be done for the assessment whether the prospective subjects are appropriate candidates for the inclusion in the studies these tests are an appropriate pre-entry activity. After obtaining the informed consent any clinical procedures can be performed for the purpose of determining the

eligibility for the research, including withdrawal from the medication (wash-out). Also, the wash-out in the preparation for the research is part of the research.

In contrast to the study related tests the procedures that are to be performed as part of the practice of the routine medicine such as for the diagnosis or the treatment of a disease or medical condition can be used for determining the study eligibility before obtaining the consent.

10. Personal Data Protection

A basic element of the data protection is the obligation imposed on the third parties not to disclose the data and keep them confidential. The confidentiality prevents the scientific community from the scrutinizing the scientific basis of a licensing decision. The confidentiality is essentially intended to protect the secret information from the misappropriation by the third parties. According to the Article 10 of the biomedicine convention "Private life and right to information":

- Everyone has the right to be respected for the private life in relation to the information about his or her health.
- Everyone is entitled to know any information collected about his or her health. However, the wishes of the individuals not to be so informed shall be observed.
- In the exceptional cases, the restrictions may be placed by law on the exercise of the rights contained in paragraph 2 in the interests of the patient.

10.1. Trial Subjects

In the accordance to the EU Directive 2001/20/EC Article 3 "Protection of clinical trial subjects" the rights of the subject to the physical and mental integrity, to the privacy and to the protection of the data concerning him has to be safeguarded. Before the subjects have been included in the clinical trial he/she has to give his/her consent for the collecting and controlling the data about his/her medical history, past and current treatments.

10.2. Data Confidentiality by Auditors

Due to the EU Directive 2001/20/EC the inspectors appointed by the Member States have to maintain the confidentiality whenever they gain access to the

confidential information as a result of the good clinical practice inspections in the accordance with the applicable national and international requirements.

Confidentiality and data access

I have bin informed of the benefit that I gain from the protection and the rights granted by the European Union Data Protection Directive and other national laws on the protection of my personal data.

I agree that the representatives of the sponsor or possibly the health authorities can have access to my medical records. My participation in the study will be treated as confidential. I will not be referred to by my name in any report of the study. My identity will not be disclosed to any person, except for the purposes described above and in the event of a medical emergency or if required by the law.

My data will be processed electronically to determine the outcome of this study, and to provide it to the health authorities. My data may be transferred to other countries (such as the USA). For these purposes the sponsor has to protect my personal information even in countries whose data privacy laws are less strict than those of this country.

_____	_____	_____
Subject Name	Place and Date	Signature

10.3. Data Confidentiality for SUSAR

During the clinical trials the SUSARs have to be reported to the competent authorities. After the processing this provided information has to be entered into the EudraVigilance database. The database of the SUSARs will contain the data relating to a specific study subjects/patients. The patient's right to confidentiality is paramount. The patient's identity in the SUSAR report forms, that enter the database, has to be codified. There is a need of the security standard as a minimum which has been required for the operation of the secure networks for the regulatory authority communication. The access to the database is restricted to:

- The competent authorities of the Member States,
- The Agency, and

- The Commission.

10.4. Investigator

During clinical trials the sponsor will collect the investigator personal data, which maybe entered into the databases and communicated to the regulatory authorities. Also, investigators have to give their permission for the transfer of these data and collection of these data.

11. Adverse Events

Adverse events (AE) or/and adverse reactions are any change in the health of the trial subjects that occur after he/she has been enrolled in a clinical trial. Not every AE is related to the treatment or test being studied, but the investigators have to report all AE's to the sponsor of the trial. Also, an AE can be declared in the normal treatment of a patient which is suspected of being caused by a medical device used in the treatment of the subject. Also, the adverse reactions are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

11.1. Serious Adverse Event

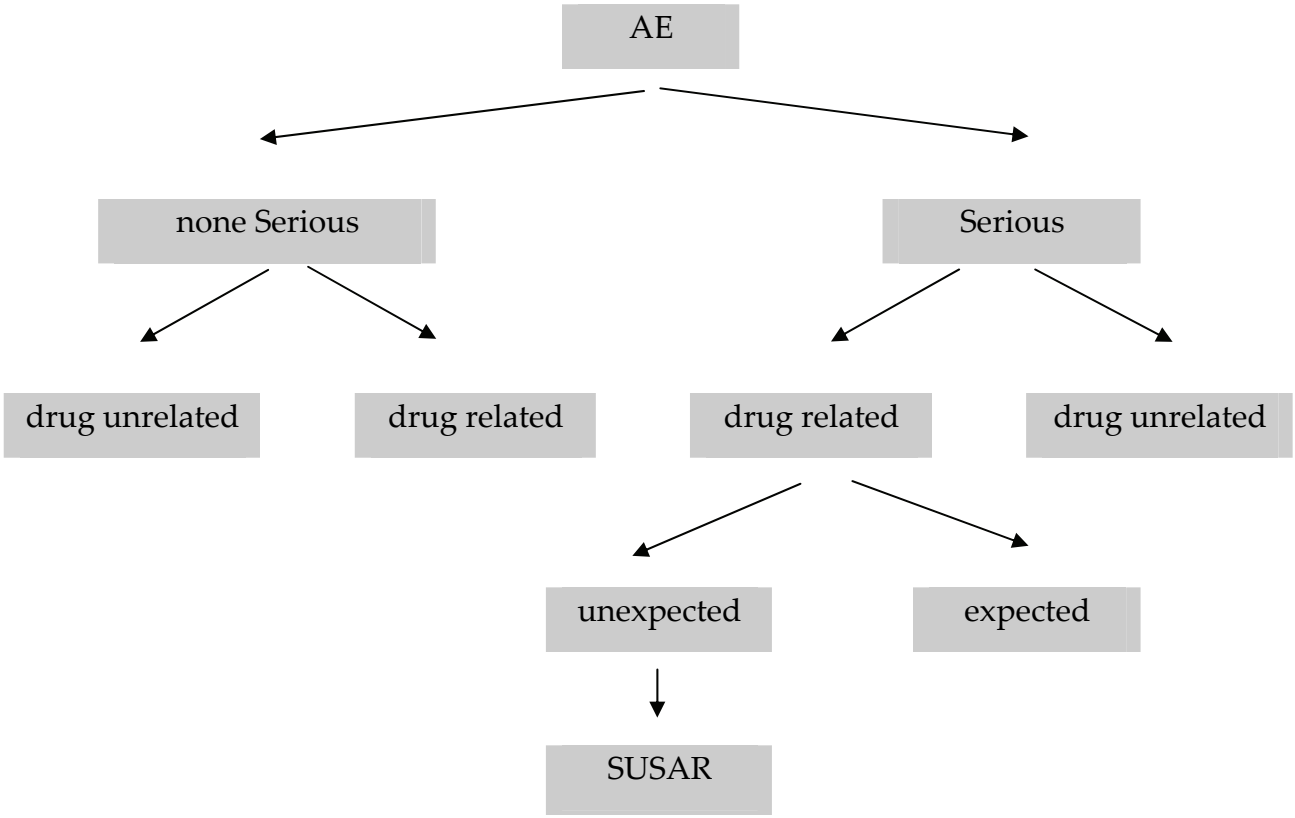
The AE or/and adverse reaction can be a serious adverse event (SAE) or serious adverse reaction. The SAE are all untoward medical occurrences or effects at any dose that:

- Resulted in the death,
- Resulted in the new inpatient hospitalisation,
- Resulted in the prolongation of the inpatient hospitalisation,
- Is life-threatening,
- Resulted in the significant disability,
- Caused the congenital anomaly or birth defect, or
- Is medically significant.

The possible cause of a SAE can be:

- The pre-existing disease,
- The underlying disease,
- The study treatment, or
- The study protocol related procedure.

The investigators have to report all SAE as soon as possible but within 24 h after the acknowledgment to the sponsor of that trial.



11.2. Suspected Unexpected Adverse Reaction

The suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction, whose nature or severity is not consistent with the applicable product information (e.g. the investigator's brochure for an unauthorised investigational product or summary of the product characteristics for an authorised product).

11.3. Responsibility of the Sponsor due to the SUSAR

In the case of a SUSAR the sponsor has to ensure that all relevant information about the SUSAR that are fatal or life-threatening is recorded and reported as soon as possible in any case no later than seven days after knowledge by the

sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days:

- To the competent authority in all concerned states,
- To the EC/IRB in all concerned states, and
- To all investigators involved in clinical trials with this medication/device.

All others SUSAR have to be reported to the competent authority, and the EC/IRB in the concerned states, and all investigators involved in the clinical trials with this medication/device as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. Further, the sponsor has to inform all competent authority, and the EC/IRB in the concerned states, and all investigators involved in the clinical trials once a year throughout the clinical trial with a listing of all SUSAR which have occurred over this period and a report of the subjects' safety.

Due to the EU guidelines the following reporting rules are applicable to all sponsors:

- As a general rule all SUSAR reports originating from any interventional clinical trial (Phase I – IV) as defined in the Directive 2001/20/EC are sent to the EudraVigilance clinical trial module.
- The sponsor makes a commitment to submit the SUSAR that qualify for reporting to the EudraVigilance, in the application to the Competent Authority of the European Economic Area Member State(s) for approval of the clinical trial.
- To avoid the double reporting to the EudraVigilance, any SUSAR case that is submitted by the sponsor to a European Economic Area Concerned Member State according to the applicable national legislation will not be forwarded by the respective Concerned Member State to the EudraVigilance.

- The sponsor has to start the SUSAR reporting to the EudraVigilance at the date of the first authorisation by any of the European Economic Area Concerned Member States of the clinical trial.
- For the clinical trials that have started before the 1st May 2004 deadline and which have at least one European Economic Area based investigator site:
  - The SUSAR should be reported to the EudraVigilance as of 1st of May 2004,
  - No retrospective reporting for the SUSAR occurring before 1st of May 2004 will be necessary, and
  - No retrospective application for a EudraCT number will be necessary.

Further, the following rules are additionally applicable only to the sponsors, who are holder of a Marketing Authorization of a product that is an investigational medicinal product in their trial:

- The SUSAR that originate from a "Non European Economic Area Country" and that qualify as the spontaneous reports in the country of the origin will nevertheless be reported to the EudraVigilance Post-Authorisation Module when the investigational medicinal product is not authorized in any European Economic Area Member State.
- The SUSAR arising from any organised data collection system other than the interventional clinical trials involving an investigational medicinal product approved in at least one European Economic Area Member State will be submitted to the EudraVigilance Post-Authorisation Module. The interventional clinical trials are defined by the Directive 2001/20/EC. The non-interventional clinical trials include the reports from the Registries and post-marketing surveillance studies/Post-authorisation Safety Studies.

11.4. Responsibility of Competent Authority due to SUSAR

The competent authority of each concerned states has to ensure that all SUSAR to an investigational medicinal product which are brought to its attention are immediately entered in a European database. Also, the Agency makes the information notified by the sponsor available to the competent authorities of the Member States.

11.5. EudraVigilance

The EudraVigilance is the clinical trial module of the TrialDataBank. It is the European data processing network and management system for the reporting and evaluation of the suspected adverse reactions during the clinical trials of the new drugs and also for following the marketing authorisation of the medicinal products.

For the quality assurance the competent authorities have access to a database, which provides each competent authority with an overview of the SUSAR linked to the investigational medicinal products used in the clinical trials being conducted in the country. This database facilitates the review of the safety of the use of these products in the clinical trials. The database also facilitates the communication on this review and the safety of these clinical trials between the authorities. This process enables the authorities to better oversee the clinical trials and the medicinal product development. Further, it provides the enhanced protection of the clinical trial subjects and patients receiving the medicinal products. The EudraVigilance has the following purposes:

- The provision of an overview of the SUSAR occurrence in all clinical trials,
- The facilitation of the communication between the competent authorities on the SUSAR,

- The generation of the signals concerning the safety of the investigational medicinal products through,
  - Its interface with the TrialDataBank, and
  - The review of the safety data in particular the populations, groups of the products, therapeutic areas etc. including the potential to generate some denominators for the safety assessment of the products,
- The review of the SUSAR including those linked with:
  - A given product trials conducted by a given sponsor,
  - A patient population type (e.g. age group, gender),
  - A product type,
  - A therapeutic category/pathology/indication,
  - A type of the reaction by frequency (e.g. frequency relative to all reports or a subset of these), and
- The generation of the statistics on the reported SUSAR.

11.5.1. Identification of Reported SUSAR

Each SUSAR will be identified by the TrialDataBank number and the sponsor protocol code number for the clinical trial involved:

- The sponsor's case number,
- The suspect product(s), and
- The study subject code.

11.5.2. Data Quality Assurance and Quality Control

It is the responsibility of the party making the data submission, coding or entry to ensure the accuracy and completeness of the data at the time it is first entered. For this purpose the responsible staffs at the sponsor and competent authority has to be trained for the data submission, validation, entry, and

review. Further, the SOP's have to be available to them. The quality control and assurance systems have to verify the accuracy, and integrity of the data entry.

11.5.3. Data Confidentiality

Access to the EudraVigilance database is restricted to the competent authorities. The database of the SUSAR contains the data relating to the specific study subjects/patients. The patient's right to the confidentiality is paramount. The patient's identity in the SUSAR report forms, that enter the database, has to be codified. Also, the personal data has to be protected in the accordance with the provisions of the GCP.

11.6. PharmacoVigilance

The PharmacoVigilance is the pharmacological science relating to the:

- Detection of the adverse effects,
- Assessment of the adverse effects,
- Understanding of the adverse effects,
- Prevention of the adverse effects, and
- Long and short term side effects of the medicine.

In general the PharmacoVigilance is the science of the collecting, monitoring, researching, assessing, and evaluating the information from the healthcare providers, and the patients on the

- Adverse effects of the biological products,
- Adverse effects of the herbal and traditional medicine, and
- Adverse effects of the medications.

The PharmacoVigilance is used for the identifying the new information about the hazards associated with the medicines, and for the preventing harm to the patients. The PharmacoVigilance is particularly concerned with the Adverse Drug Reactions. While the clinical trials involve several thousand patients, the less common side effects and Adverse Drug Reactions are often unknown at the time a the drug enters the market. After entering the market the data about the Adverse Drug Reaction will be collected. Also, the post marketing PharmacoVigilance uses the tools such as the data mining, and investigation of the case reports to identify the relationships between the drugs and the Adverse Drug Reactions.

11.6.1. Spontaneous Reporting

The spontaneous reporting is the core data-generating system of the international PharmacoVigilance, relying on the healthcare professionals to identify, and report any suspected Adverse Drug Reaction to their national PharmacoVigilance centre, or to the manufacturer. The spontaneous reports are always submitted voluntary. One of the system's major weaknesses is the under-reporting. Also, the problem with this voluntary system is that the hard-pressed medical personnel don't always see it as a priority. There are two possible problems:

- When the effects are not serious, the medical personnel may not get to know about them, or
- When the effects are serious, the medical personnel may not be recognised as the effect of the drugs.

The spontaneous reports are a crucial element in the worldwide enterprise of the PharmacoVigilance, and form the core of the WHO Database.

11.7. Manufacturer and User Facility Device Experience Database

In the USA the FDA provides a database for reporting of the AE call the Manufacturer and User Facility Device Experience Database (MAUDE). The MAUDE data represents the reports of the AE involving the medical devices. The MAUDE will be updated quarterly. The MAUDE data is not intended to be used either to evaluate the rates of the AE or to compare the AE occurrence rates across the devices.

http://www.fda.gov/cdrh/maude.html

11.8. Reports of Efficacy and Safety Studies

The clinical trials will prove the therapeutic values of the medicinal products. The treatment of the control groups will vary from the case to case and also will depend on the ethical considerations and the therapeutic area. The safety data will be reviewed with the particular attention to the events resulting in:

- The changes of the dose or need for the concomitant medication,
- The SAE, and
- The events resulting in the withdrawal and deaths of the subjects.

11.9. Reports of Post-Marketing Experience

If the medicinal product is already authorised in the third countries, the information has to be collected in respect of the adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

11.10. International Society of PharmacoVigilance

The International Society of PharmacoVigilance (ISoP) is an international non-profit scientific organisation, which aims to foster the PharmacoVigilance both

scientifically and educationally, and enhance all aspects of the safe and proper use of the medicines, in all countries. The ISoP was first conceived as a European society (ESoP) in 1992. The 2005 Annual Meeting, the first international PharmacoVigilance meeting in the Far East, was in Manila. In 2008 the annual meeting will be held in Buenos Aires. Following objectives are intended to be met by the ISoP:

- Encouraging and extending the research in the field of the PharmacoVigilance,
- Promoting a regular exchange of the information bearing on the PharmacoVigilance,
- Encouraging the education in the PharmacoVigilance at all levels,
- Cooperation with the other organizations and societies concerned with the PharmacoVigilance,
- Publishing the scientific and other relevant aspects of the PharmacoVigilance,
- Engaging in other activities which are pertinent to the PharmacoVigilance, and
- Seeking funds, and awarding grants to promote the PharmacoVigilance,

The ISoP's aim is to promote all these aspects of the drug safety:

- The safer drug design, and
- The safer drug usage at the collective and individual level.

11.11. International PharmacoVigilance

The principal of the international collaboration in the field of the PharmacoVigilance is the principle basis for the WHO International Drug

Monitoring[28]. The member countries send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database[29]. When there are several reports of the adverse reactions to a particular drug this process may lead to the detection of a signal – an alert about a possible hazard communicated to the member countries. This will only happen after the detailed evaluation and the expert review.

[28] The WHO Programme for the International Drug Monitoring provides a forum for the WHO member states to collaborate in the monitoring of the drug safety. Within the Programme, the individual case reports of the suspected adverse drug reactions are collected and stored in a common database, presently containing over 3.7 million case reports.

[29] The WHO database holds more than 3,000,000 individual case safety reports contributed by the National Centres participating in the WHO International Drug Monitoring Programme. The WHO Programme started in 1968, with 10 countries providing the data from the national spontaneous reporting systems. In 1978 the operational responsibility for the Programme was transferred from Geneva, to a WHO Collaborating Centre in Uppsala, Sweden. The centre is now known under its field name the Uppsala Monitoring Centre (UMC). http://www.who-umc.org/

12. Monitoring

The International Organization for Standardization (ISO)[30] defines a monitor as a "qualified person appointed by the sponsor responsible for ensuring the investigator's compliance with the clinical investigation plan and for the reporting on the progress of the clinical investigation." In the United States, the Food and Drug Administration (FDA), defines a monitor as an "individual designated by a sponsor or contract research organization to oversee the progress of an investigation." According to the European Committee for Standardization (CEN)[31], a monitor is "a person appointed by the sponsor and responsible to him for monitoring and reporting on the progress of the clinical investigation."

12.1. Monitor Responsibilities

The monitor's specific responsibilities vary from country to country. The monitor's responsibilities fall into three broad responsibility categories:

- Ensuring the protocol compliance with
  - The Declaration of Helsinki,
  - The applicable FDA regulations, and
  - The legal requirements of the national authorities,
- Ensuring the protection of the rights, safety, and welfare of the subjects, and
- Ensuring the data integrity.

[30] ISO is an international standard-setting body composed of the representatives from the various national standard bodies.

[31] CEN is a non-profit organisation whose mission is to foster the European economy in the global trading, the welfare of the European citizens and the environment by providing an efficient infrastructure to the interested parties for the development, maintenance and distribution of the coherent sets of the standards and specifications.

Also, the monitors play a critical role in initiating and conducting the clinical trials. They serve as the primary liaison and the communication link between the sponsor and the investigators. They manage the day-to-day activity of the trial. They tackle all of the problems that arise at the investigator's site, most of the problems that arise with the protocol or CRF, and many of the problems that arise with the IMP. The monitors have to:

- Confirm that the investigator understands the study,
- Check the protocol compliance and notify the sponsor of the deviations,
- Confirm the ongoing site qualification,
- Verify that the proper procedures are in place for reporting the adverse events and effects,
- Ensure the consistency between the CRF data and the subject files, and
- Confirm that the informed consent is obtained.

The monitor duties are organized around the specific types of the site visits:

- The site selection visit,
- The study initiation visit,
- The study monitoring visit, and
- The closeout visit.

12.1.1. Site Selection Visit

The monitor has to conduct the site selection visit. The purpose of this visit is the selection of the investigators and the investigative sites. The objective is to determine whether the investigator is qualified by the training and experience to conduct the investigation.

12.1.2. Study Initiation Visit

The monitor has to conduct an initiation visit any time within a month or so of starting the study. The study initiation visit may take some time, often four hours or so. The monitor has to plan a page-by-page review of the protocol, informed consent forms, CRFs, and investigator's brochure, noting any areas of the potential confusion or non-conformance.

12.1.3. Study monitoring visit

During the clinical trial the monitor has to visit the trial site. The exact visit frequency is depending on the number of the subjects enrolled on the study. Also, the first monitoring visit has to occur after the first subject has been enrolled in the trial.

12.1.4. Closeout Visit

The monitor's final responsibility is the study closeout visit. The purpose of this visit is to resolve the remaining issues at the end of the study and bring the trial to a close. During the closeout visit, the monitor reviews the investigator's file for the last time, making sure it is complete and up-to-date. They balance the device or the drug accountability log, and ship the remaining study articles to the sponsor.

12.2. Monitoring Visit Activities

The routine monitoring visits are the heart of the study monitoring. The monitor has to read the last monitoring report, the previously reported SAE's and all other relevant correspondence. Further, the monitor needs following documents for a monitoring visit:

- The personal tracking forms,
- The discrepancy reports,

- The record of the missing CRF pages,
- The record of the outstanding queries from the previous monitoring visits, and
- The SAE reports needing verification.

For an acceptable result the monitoring visit has to be prepared by:

- Making appointments with the appropriate staff at the site,
- Scheduling sufficient time for the site ,
- Confirming, which source documents are needed,
- Preparing a monitoring visit checklist,
- Checking the trial medication will be accessible, and
- Bringing any additional necessary study documents.

The first step in the monitoring a site is to check the overall study progress. Following questions are to be answered during the monitoring visit:

- Is the knowledge of the staff up-to-date or need they additional training?
- Are the subject enrolments proceeding as expected?
- Does the site need additional e.g. CRF, Laboratory materials, IMP?
- Is it necessary to meet the principal investigator personally for a few minutes?

During the monitoring visit the monitor has to check the following study documents:

- The investigator files,
  - The presence of the last dated, and approved copies of the study protocol,
  - The presence of the last versions of the consent forms,
  - The presence of any approved amendments,
  - The presence of the last version of the Investigator's Brochure,
  - The presence of the update certification of the laboratories performing the tests or procedures,

- The list of the persons authorized to enter the data on the CRF's,
- The subject screening and tracking log,
- The log matching the subjects' data and their identification numbers,
- The study drug accountability log, accounting for every investigational article delivered to the site and recording its dispensation,
- The copies of all serious adverse event reports, and
- The copies of all annual reports.

- The case report forms,
  - For ensuring the data integrity,
  - For confirming that the transcription of the data from the source files to the CRF's is complete, accurate, legible, and logical, and
  - For ensuring that there are no omissions of the entries (such as unrecorded concomitant illnesses).
- Resolving the outstanding queries with the site.
- The source documents,
  - The patient history and physical examination forms,
  - The laboratory records,
  - The pharmacy records,
  - The X-rays, CT-scans, radiology reports,
  - The ultra sound, echocardiography reports,
  - The ECG examinations,
  - The Pathological- and Histological-Reports,
  - The physicians orders,
  - The nurse records,
  - The study personal records,
  - The documentation of informed consent and study participation in the patient records, and
  - The patient diaries.

- The signed informed consent by the patient.
- Ensuring the randomization compliance.
- Verification that the patient entry to the study matches the inclusion and exclusion criteria.
- The drug storage.

The monitor has to discuss any new development on the project, number of the subjects enrolled, and the status of the study or problems. The status of the subjects on the study has to be discussed with the site. The monitor has to collect the information about the SAE's and if they are reported appropriately. At the end of the monitoring visit the monitor has to discuss the following points with the responsible person at the site:

- The recruitment issues at the site,
- The protocol violations/deviations,
- The significant issues related to the source documentation,
- The significant issues related to the CRF completion,
- The significant issues related to the informed consent,
- The data flow and difficulties,
- The study drop-outs,
- The reported and unreported adverse events,
- The problems with the drug accountability,
- The problems with the drug compliance, and
- The missing patient visits, procedures or samples.

The monitor has to send to the trial centre a follow-up letter with the brief overview of the study visit activities. In particular, the document problems encountered and solutions discussed.

12.3. Monitor Qualification

Most monitors were trained as the nurses, but musicians, engineers, statisticians, biologists, epidemiologists, microbiologists, and computer scientists have all become successful and effective monitors. The monitors should be knowledgeable about their company's SOP and work in conformity with them. They should take part in the ongoing training activities to keep their knowledge up-to-date. The most important quality for a monitor is a commitment to accuracy, completeness, and logic. The monitors qualification can be determined by:

- The complexity of the study,
- The nature of the disease or condition under the study,
- The number of the investigators conducting,
- The number of the sites, and
- The type of the product involved.

12.4. Professionalism in Monitoring

For ensuring that the clinical trials are conducted by the high quality standards, the monitors have to:

- Be familiar with the trial, which include,
  - The study protocol,
  - The CRF,
  - The Investigator's Brochure,
  - The study associated measurements, and
  - All other relevant documents and associated forms,
- Be well organized,
- Ensure that the ICH-GCP guidelines are being followed,
- Ensure that the investigator is well informed about the study procedures,
- Ensure that sufficient study documents are available at the site,

- Ensure that the drug accountability is performed,
- Ensure that sufficient non-expired drug is available at the site,
- Document all necessary steps for the site,
- Document all relevant information for the file notes, and
- Document all relevant information for the monitoring report.

12.5. Frequency of Monitoring Visits

The first monitoring visit has to occur after the first subject has been enrolled in the trial. The subsequent monitoring visits should occur at the regular intervals. However, the exact visit frequency is depending on the number of the patients enrolled on the study. Following monitoring visits has to be conducted:

- The first monitoring visit. Within 10-30 working days of the enrolment of the first patient into the study at the site.
- Further monitoring visits has to occur during the treatment, and depends form the number enrolled by the site.
- The last monitoring visit has to occur after all queries are resolved and all data are collected.

12.6. Maintaining Contact

When the frequent on-site monitoring is not needed, the monitor has to maintain contact to the site by e.g. phone and mail. The significant information given by the site has to be documented via a file note or telephone report. The best way is to maintain the contacts with the sites once per month if no monitoring has been for seen.

12.7. Monitoring log

The monitor has to document his site visit on a monitoring log. It has been placed in the investigator file.

12.8. FDA Guideline for the Monitoring

The FDA guideline (21 CFR 10.90) is not a legal requirement but represent a standard of practice that is acceptable to the FDA. Due to this guideline the procedures for the monitoring a clinical investigation selected by the sponsors can be submitted (it is not required) to the FDA for review. This procedure will ensure to avoid the possibility of employing the monitoring procedures that the FDA might later determine as to be inadequate.

Selection of a Monitor

- The appropriately trained and qualified individuals,
- The physicians, veterinarians, clinical research associates, paramedical personnel, nurses, and engineers are the acceptable monitors depending on the type of the product involved in the study, and
- A monitor need not to be a person qualified to diagnose and treat the disease or other condition for which the test article is under the investigation.

➢ The considered factors in determining the number of the monitors

- The number of the investigators conducting the study,
- The number and location of the facilities in which the study is being conducted,
- The type of the product involved in the study,
- The complexity of the study, and
- The nature of the disease or other condition under the study.

➢ The Written Monitoring Procedures

- The written procedures for monitoring the clinical investigations to assure:

- The quality of the study, and
- That each person involved in the monitoring process carries out his or her duties, and

- A standardized, written procedure, sufficiently detailed to cover the general aspects of the clinical investigations.

➢ The Pre-investigation Visits

- To assure that the investigator clearly understands and accepts the obligations incurred in undertaking a clinical investigation, through the personal contact between the monitor and each investigator,
- To visit the site prior to the initiation of a clinical investigation for assuring that the investigator:
  - Understands the investigational status of the test article and the requirements for this accountability,
  - Understands the nature of the protocol or investigational plan,
  - Understands the requirements for an adequate and well-controlled study,
  - Understands and accepts his or her obligations to obtain the informed consent in accordance with the ICH-GCP,
  - Understands and accepts his or her obligation to obtain the EC/IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure the continuing review of the study by the EC/IRB in accordance with the 21 CFR Part 56, and to keep the sponsor informed of such EC/IRB approval and subsequent the EC/IRB actions concerning the study,
- To assure that the investigator has access to an adequate number of suitable subjects to conduct the investigation,
- To assure that the investigator has adequate facilities for conducting the clinical investigation, and

- To assure that the investigator has sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by the applicable regulations.

➢ The Periodic Visits

- Responsible for assuring throughout the clinical investigation that,
- The investigator's obligations, as forth in the applicable regulations, are being fulfilled,
- The facilities used in the clinical investigation continue to be acceptable,
- Maintaining personal contact between the monitor and the investigator throughout the clinical investigation frequently enough to assure that:
  - The facilities used by the investigator continue to be acceptable for purposes of the study,
  - The study protocol or investigational plan is being followed,
  - The changes to the protocol have been approved by the EC/IRB and/or reported to the sponsor and the EC/IRB,
  - The accurate, complete, and current records are being maintained,
  - The accurate, complete, and timely reports are being made to the sponsor and the EC/IRB, and
  - The investigator is carrying out the agreed-upon activities and has not delegated them to the other previously unspecified staff.

➢ The Review of the Subject Records

- Responsible for assuring that the data submitted to the FDA in support of the safety and effectiveness of a test article are accurate and complete,
- Review the individual subject records and other supporting documents and compare those records with the reports prepared by the investigator for submission to the sponsor,
- Compare a representative number of the subject records and other supporting documents with the investigator's reports to determine that:

- The information recorded in the investigator's report is complete, accurate, and legible,
- There are no omissions in the reports of the specific data elements such as the administration to any subject of the concomitant test articles or the development of an inter-current illness,
- The missing visits or examinations are noted in the reports,
- The subjects failing to complete the study and the reason for each failure are noted in the reports, and
- Informed consent has been documented in the accordance with the 21 CFR Parts 50 and 56 (ICH-GCP Guideline).

➢ The Record of the On-Site Visits

- Maintaining a record of the findings, conclusions, and action taken to correct the deficiencies for each on-site visit to an investigator. The record may include such elements as:
  - The date of the visit,
  - The name of the individual who conducted the visit,
  - The name and address of the investigator visited.
  - A statement of the findings, conclusions and any actions taken to correct any deficiencies noted during the visit, and
- Such a record may enable the FDA to determine that a sponsor's obligations in monitoring the progress of a clinical investigation are being fulfilled.

13. Audit (Inspection)

The audit means the evaluation of an organization, system, process, project or product. In the clinical trial an audit is an independent assessment to ascertain the validity and reliability of the collected data. It is performed by the competent, independent and objective person or persons, known as the inspectors/auditors. During and after the end of the clinical trial the inspections by the competent authority, and/or the sponsor will be performed for an official review of

- The documents,
- The facilities,
- The records,
- The quality assurance arrangements, and
- Any other resources that are deemed by the competent authority, and/or by the sponsor to be related to the clinical trial and that may be located
  - At the site of the trial,
  - At the clinical trial units of the sponsor, and/or the contract research organisation's facilities, or
  - At the other establishments.

Due to the EU Directive 2001/20/EC GCP the inspections may take place on any of the following occasions:

- Before the conduction of the clinical trials,
- During the conduction of the clinical trials,
- After the conduction of the clinical trials,
- As part of the verification of the applications for the marketing authorisation, and
- As a follow-up to the granting of the authorisation.

The audits will affect changes in:

- The national, and international regulations,
- Improve the quality, and
- Establish the consistency.

The regulatory bodies will perform the audits on:

- The clinical trial sites,
- The EC/IRB, and
- The sponsor facilities.

Due to the regulatory affairs the following authorities can perform the audits:

- The national regulatory bodies,
- The FDA,
- The EMEA, and
- The country specific authorities.

The audits performed by the sponsor are two different types:

- Internal,
  - To prove the own systems, procedures, and facilities, and
- External
  - To prove the subcontractors, and
  - To prove the clinical trial sites.

13.1. Internal Audits

The internal audits will be performed by the internal auditors who are the employees of the company quality assurance department for assessing and evaluating its system of the internal control. To maintain their independence, they present their reports directly to the Board of Directors or to the Top Management of the sponsor. The subjects of the internal audits are:

- To ensure the compliance with the companies SOP's,
- To propose any corrective and preventive action,
- To spread the message, that the quality is everyone's responsibility,
- To catalyze the continuous improvement, and
- To ensure the fulfilment of the regulatory requirements.

The frequency of the internal audits can differ in every organisation it depends on:

- The size, and complexity of the organization,
- The responsibility for the management,
- The necessity to provide the valuable preparation for the regulatory audits,
- The necessity to check for the records of the previous audits,
- The necessity to review the effectiveness of the Plan-Do-Check-Act cycle,
- The necessity to review the SOP's,
- The necessity to review the essential documents, and
- The necessity to review the qualifications of the staff.

13.2. External Audits

The external audits will be performed by the extern auditors who are the employees of a quality assurance company or they are from the regulatory authorities. The subjects of the regulatory audits are:

- To ensure the regulatory compliance,
- General and/or specific in nature,
- Mutually recognizing the audit findings from other regulatory bodies, and
- Different considerably in the scope, frequency and duration.

13.3. Audit Process

During the audit process the verification of the compliance with the standards of the ICH-GCP and the need to the subject data, information and documents to the inspection in order to confirm that they have been properly generated, recorded and reported are essential in the clinical trials. For this reason the different documents will be reviewed and a lot of the aspects will be discussed with the key personal. The following points will be reviewed e.g.:

- The documentation,
- The reports from the prior audit,
- The training material and confirmation of the training,
- The technology validation and the maintenance used by the company or the sites,
- The appropriate staffing and their qualifications, and
- The specification of the test article.

During the audit process at the study sites the following points has to be reviewed and ensured by the auditors:

- The right and safety of the study subjects,
- The integrity of the collected data,
- The compliance with the regulatory requirements, and
- The compliance with the protocol requirements.

13.4. Work Steps during Audit Process at Trial Site

By starting the audit process the auditor has to interview the key personals on the site for ensuring their knowledge about the trial, recruiting process, randomisations, and difficulties. The following point has to be reviewed by the auditors:

- The involvement of the investigator on the study,

- The delegated responsibilities,
- The knowledge of other involved personals,
- The informed consent process,
- The investigator site file for the completeness:
  - The recent consent form (all other versions),
  - The subject identification list,
  - The randomisation documents,
  - The current protocol and all amendments,
  - The monitor log and the correspondence, and
  - The financial payments,
- The CRF entries,
- The source documents support the data in the CRF,
- The availability of all sources for the records,
- The source documents are:
  - Attributable,
  - Legible,
  - Contemporaneous,
  - Original, and
  - Accurate,
- The Electronic Data Capture:
  - The source data are in consent with the documentation provided by the investigator,
  - The query systems,
  - The file structure and merger of the data sets,
  - The validation methods and documentation, and
  - The fulfilment of the fundamental elements of the quality whether collected or recorded electronically or on the paper.

13.5. Audit Questions

Before starting the audit the following key questions have to be discussed by the auditors.

- When is the right time point to the audit?
- What regulations impact the audit process?
- Where has to be audited?
- Who has to be interviewed?
- What information has to be collected?
- When was the last audit?
- Which qualifications need the auditors?

13.6. FDA-Findings

The FDA list of the common deficiencies when inspecting the sponsor monitors, and the CRO activities:

- The failure to ensure the proper monitoring of the clinical investigation,
- The failure to ensure the investigator compliance,
- The failure to provide the accurate, complete and current information,
- The failure to provide the investigators with the information they need to conduct the investigation properly,
- The failure to maintain the complete accountability records,
- The failure to maintain the control of the test article, and
- The promotion of the test article in a prohibited manner.

13.7. Notification of Inspection to National Agency

The National Agency for Medicines is the supervisory authority for the clinical trials on the medicinal products. The Agency has to be provided with any

clarifications that it needs to perform this supervision. The Agency has the right to inspect any aspect necessary, including the trial site, the trial documents and the patient documents concerning the trial subjects. If a foreign authority intends to inspect the trial site and the trial documents, the sponsor has to report the inspection to the National Agency for Medicines by the letter within seven days after the sponsor was informed of the intended inspection.

13.8. Disqualification of Investigators by FDA

The clinical investigators could be disqualified by the FDA:

- When the investigator has repeatedly or deliberately violated the Agency's regulations, and/or
- When the investigator has submitted the false information to the sponsor in a required report.

In these cases the appropriate FDA Centre will send the investigator a written notice and offer the investigator an opportunity to respond to the notice in a specify time period at an informal conference or in writing. If the investigator offers a timely and satisfactory explanation for the non-compliance the process will be terminated. Also, the investigator will be notified in the written form. In the case of the rejection the FDA will offer the investigator an opportunity for an informal regulatory hearing to determine whether the investigator should remain eligible to receive the investigational test articles.

13.9. Suspension of Clinical Trial by Competent Authority

The competent authorities can suspend or prohibit a clinical trial where it has the objective grounds for considering:

- The conditions in the authorisation are not being met,
- The doubts about the safety or scientific validity of the clinical trial, and
- The raising safety issues.

In these cases the competent authority will inform the sponsor, and ask them for their opinion. The sponsor has immediately to investigate the grounds for the suspension or prohibition, and to provide a report within one week addressing the issues raised. In the case of the imminent risks for the trial subjects the competent authority will suspend the trial immediately.

13.10. Clinical Trial Audit Process

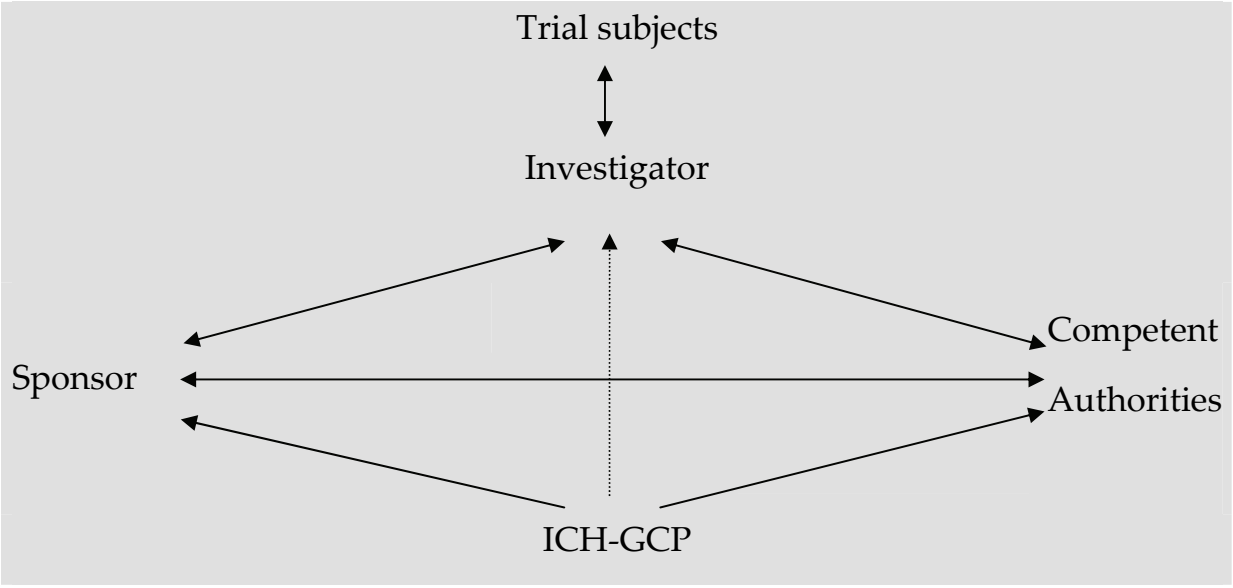
The audit process in the clinical trial sites seeks to identify the areas for the improvement, develop and carry out the action plans to rectify or improve the processes. In a second audit the auditor will ensure that these changes have an effect. Due to this process a higher level of the quality will be reached by the sites. The clinical audit process can be divided in 5 steps:

- To identify the problems,
- To define the criteria and standards,
- To collect data,
- To compare the performance with the criteria and standards, and
- To implement the changes.

14. Quality Assurance

The concept of the quality assurance has been evolved from the inspection, measurement, and testing, which had been in the practice for many, many years. The quality, as a profession and the managerial process associated with the quality function, was introduced during the second-half of the 20th century, and has evolved since then. No other profession has seen as many changes as the quality profession. The quality profession grew from the simple control, to the engineering, and the system engineering. The quality control activities were predominant in the 1940s, 1950s, and 1960s. The 1970s were an era of the quality engineering and the 1990s saw the quality systems as an emerging field. Like the medicine, accounting, and engineering, the quality has achieved status as a recognized profession.

The Interactions between the factors that is important for the quality during the clinical trials.



During the clinical trial the quality of the collected data plays a crucial role for success. For the quality assurance it is either the correctness of the collected data or the completeness of the data crucial. While it is impossible to improve

the quality afterwards the adequately quality assurance programs have to be implemented before and during the conduction of the clinical trial.

- The collection of the right data.
- The high quality of the collected data.
- The GCP conformed data collection.

14.1. Management Responsibility for Pharmaceutical Quality System

Due to the ICH Q10 "PHARMACEUTICAL QUALITY SYSTEM" dated 9. May 2007 the leadership is essential to establish and maintain a company-wide commitment to the quality and for the performance of the pharmaceutical quality system. Some points are:

- The Management Commitment,
  - The ultimate responsibility to ensure an effective pharmaceutical quality system in place,
  - The defined responsibilities and authorities,
  - The communication and implementation throughout the company,
  - The participation in the design, implementation and monitoring of the pharmaceutical quality system,
  - The definition and communication individual and collective roles, responsibilities and authorities of all organizational units related to the pharmaceutical quality system,
  - Ensuring that the interactions are defined and understood,
  - Advocate the continual improvement, and
  - Commitment of the appropriate resources.
- The Quality Policy,
  - Establishing a quality policy that describes the overall intentions and direction of the company related to the quality,

- Inclusion an expectation to comply with the applicable regulatory requirements and facilitate the continual improvement of the pharmaceutical quality system, and
- Reviewing periodically for the continuing effectiveness.

➢ The Quality Planning,

- Ensuring that the quality objectives needed to implement the quality policy are defined and communicated,
- Support of the quality objectives by all relevant levels of the company, and
- Providing the appropriate resources and training to achieve the quality objectives.

➢ The Resource Management,

- Determining and providing the adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness, and
- Ensuring that the resources are appropriately applied to a specific product, process or site.

➢ The Internal Communication,

- Ensure establishing and implementation of the appropriate communication processes within the organization,
- Ensure the flow of the appropriate information between all levels of the company, and
- Ensure the escalation of the certain product quality and pharmaceutical quality system issues to the appropriate levels of the management in a timely manner.

➢ The Management Review,

- Responsible for the pharmaceutical quality system governance through the management review to ensure its continuing suitability and effectiveness.

➢ The Oversight of the Outsourced Activities,

- Oversight and review of the outsourced activities, and
- Specification of the responsibilities for the quality-related activities of the contract giver and contract acceptor in the written agreement.

14.2. Project Planning and Implementation

The Plan, Do, Check, Act (PDCA) cycle has to be repeatedly implemented, as quickly as possible, in the upward spirals that converge on the ultimate goal, each cycle closer than the previous. The PDCA was made popular by Deming[32]. It is better to be approximately right than exactly wrong. Over time and with better knowledge and skills, the PDCA will help define the ideal goal, as well as to help get there.

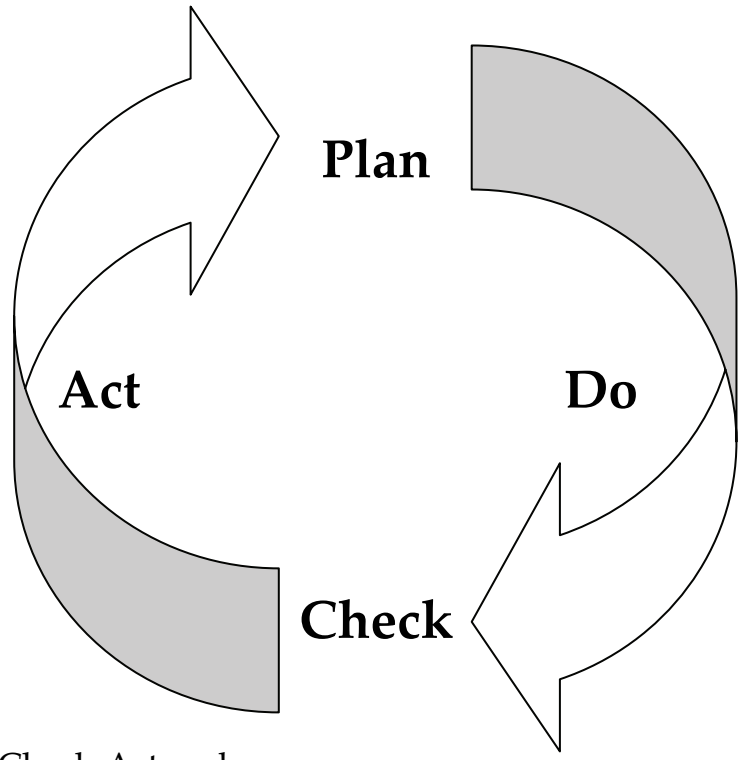
➢ Plan means the objectives and processes necessary to deliver the results in accordance with the specification.

➢ Do mean implementation of the processes.

➢ Check mean monitor and evaluate the processes and results against the objectives and specifications and report the outcome.

➢ Act means apply the actions to the outcome for the necessary improvement. After reviewing all steps (Plan, Do, Check, Act) and the process has to be modified and improved before its next implementation.

[32] Dr. William Edwards Deming (1900-1993 USA) was a statistician, college professor, author, lecturer, and consultant. He is widely credited with the improving production.



The Plan-Do-Check-Act cycle

In the Six Sigma[33] programs, this PDCA cycle is called Define, Measure, Analyze, Improve, and Control (DMAIC):

- Define the process improvement goals that are consistent with the customer demands and the enterprise strategy.
- Measure the current process and collect the relevant data for the future comparison.
- Analyze to verify the relationship and causality of the factors. Determine what the relationship is, and attempt to ensure that all factors have been considered.
- Improve or optimize the process based upon the analysis.
- Control to ensure that any variances are corrected before they result in defects.

[33] "Six Sigma" is a system of the practices to systematically improve the processes by the eliminating the defects. Since its development it has become an element of many Total Quality Management initiatives.

14.3. Standard Operating Procedure

A standard operating procedure (SOP) is a set of the instructions having the force of a directive, covering those features of the operations that lend themselves to a definite or standardized procedure without loss of the effectiveness. Also, the SOP's are detailed, written instructions to achieve uniformity of the performance of a specific function.

14.4. Quality Risk Management

The risk management principles are effectively utilized in many areas of the business and government including the finance, insurance, occupational safety, public health, PharmacoVigilance, and by the agencies regulating these industries. The goals of an overall risk management program have been to

- Identify the areas of the actual or potential risk,
- Prevent, as much as possible, the injuries to the patients, visitors and employees, and
- Prevent or limit the financial loss to the hospital and its staff.

The manufacturing and use of a medicinal product necessarily entail some degree of the risk. The risk to its quality is just one component of the overall risk. It is important to maintain the product quality throughout the product lifecycle. An effective quality risk management approach can further ensure the high quality of the medicinal drug to the patient by providing a proactive means to identify and control the potential quality issues during the development and manufacturing. Additionally, use of the quality risk management can improve the decision making if a quality problem arises. The quality risk manager is charged with:

- Identifying the potential losses,

- Evaluating the potential losses,
- Selecting the appropriate technique or combination of the techniques for treating the loss exposures, and
- Administering the risk management program.

The effective quality risk management can:

- Facilitate better and more the informed decisions,
- Provide the regulators with greater assurance of a company's ability to deal with the potential risks, and
- Beneficially affect the extent and level of the direct regulatory oversight.

14.5. Data Quality

The quality of the data refers to the quality of the collected data. It is high if they are fit for their intended uses in the decision making and planning. There are a considerable amount of the data quality research that involves investigating and describing the various categories of the desirable attributes of the data.

14.6. Data Cleaning

The data cleaning is the act of detecting and correcting (or removing) the corrupt or inaccurate records from a record set. The actual process of the data cleaning may involve removing the typos or validating and correcting the values against a known list of the entities. The inconsistencies detected or removed may have been originally caused by the different data dictionary definitions of the similar entities in the different stores, may have been caused by the user entry errors, or may have been corrupted in the transmission or storage.

14.7. Data Validation

The data validation is the process of ensuring that a program operates on the clean, correct and useful data. It uses routines that check for correctness or meaningfulness of the data that are entered to the system. The methods used for the validation are e.g.

- The format check. The data has to be checked for the specified format.
- The data type checks. The data type of the input has to be checked for an error message if the input data does not match with the chosen data type e.g. in an input box accepting the numeric data, if the letter 'O' was typed instead of the number zero, an error message would appear.
- The range check. The data has to be checked for lying within a specified range of the values e.g. the month of a person's date of the birth should lies between 1 and 12.
- The limit check. The data has to be checked for one limit only, upper or lower e.g. the data should not be lower than 1 (<1).
- The presence check. The data has to be checked for the presence of the important data and that the data have not been missed out e.g. the subject age.
- The check digits. Used for the numerical data.
- The batch totals. The data has to be checked for the missing records. The numerical fields may be added together for all records in a batch.
- The spelling check. The data has to be checked for the spelling and grammar errors.
- The consistency checks. The fields have to be checked for ensuring that the data in these fields corresponds, e.g., If Title = "Mr.", then Gender = "M".

15. Investigational Drug

Investigational drug is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes the products without any marketing authorisation and the products already with a marketing authorisation:

- Used or assembled (formulated or packaged) in a way different from the authorised form,
- Used for an unauthorised indication, or
- Used to gain further information about the authorised form.

After an IND is in effect in the case of the FDA (21 CFR312.40) or an authorisation has been received from the competent authority the sponsor can ship the study drug to the clinical sites.

15.1. Supply of Medicinal Products

The wholesale distributor, a hospital pharmacy, or a pharmacy may supply the investigator with the IMP for a clinical trial. If the trial is conducted at a hospital, the information on the IMP received has also to be given to the hospital pharmacy, or the responsible study coordinator. The responsible person for the storage of the IMP has to acknowledge the receipt of the products by

- Fax,
- Letter,
- Internet, or
- IVRS.

15.2. Documentation of Medicinal Products Use

The sponsor and the investigator site have to keep a record stating the delivery, receipt, use, return and destruction of the IMP. The trial subject has to be provided with the IMP and any equipment needed for their use without charge, unless there is the justifiable reason for acting otherwise.

15.3. Cost of Medicinal Products

The trial subject has to be provided with the IMP and any equipment needed for their use without charge, unless there is justifiable reason for acting otherwise. In any case, when the sponsor is interested to use a specific comparator the sponsor has to provide the investigators with this specific comparator.

15.4. Drug Delivery and Administration

For a medication to be effective, first it needs to reach a target location in the organism. Some type of the delivery system is needed for this to occur. This requires the use of a specific route of the administration. Three major routes are used for the drug delivery:

- The topical route,
- The enteral route, and
- The parenteral route.

15.4.1. Topical Route

The topical route (cutaneous) can be used to apply a drug for its local activity at the area of the application. The drugs may also be applied topically (transcoutaneous) to a site from which they can be absorbed to exert a systemic effect. The vaginal creams are examples of the topical drugs used in

contact with the mucous membranes rather than the epidermis. The topical drugs are also used for the eye (ophthalmic), ear (otic), and nose (intranasal). Finally, certain topical drugs can be delivered into the lung (inhalation) for both the local and systemic effects.

15.4.2. Enteral Route

The most common and convenient route for the drug administration is via the gastrointestinal tract. The oral route (per os, PO) is the most common enteral route. The medication may be administered:

- Sublingually (SL). Using the tablets formulated for the SL administration.
- Buccally. In contact with the oropharyngeal mucosa, as in the case of the nystatin oral suspension.

When the medication is given via the gastrointestinal tract, the mechanisms usually involved in the absorption of the nutrients are "borrowed" to transport the drug in the body. In fact the gastrointestinal tract takes on an added function. This is because the absorbable drugs have some chemical features in common with the nutrients. Each oral dosage form possesses the unique pharmaceutical characteristics that define the manner in which the drug is released and where and how it is absorbed. Alterations in the dosage form may interfere with a drug's efficacy, potency, or tolerance.

15.4.3. Parenteral Route

The most invasive route for the drug administration is the parenteral route. Parenteral means not via the gastrointestinal tract, it is commonly used to refer to the routes requiring some form of the injections. The routes include the injection into the blood stream, most commonly intravenously (IV), or into a vein. Intravenous injection can be done rapidly (IV push), over a limited time

(IV piggyback), or over a longer time (IV infusion). Occasionally, the blood vessel may be an artery instead of a vein. The Arteries sometimes are used as the injection site for the provision of the intra hepatic chemotherapy (intra arterial injection). Also, the medication can be injected:

- Into the subcutaneous tissue (SQ),
- Into the muscle tissue (IM),
- Into the skin (intra dermal),
- Into the spinal canal,[34]
- Into the dura surrounding the spinal cord,[35]
- Into the space within a joint,[36]
- Slow infusion subcutaneously,[37]
- Into the peritoneum (intraperitoneal),
- Into the wall of the heart or into one of its chambers (intracardiac),[38]
- Into the trachea (intratracheal),[39]
- Into the ventricles of the brain (intraventricular),[40]
- Into the amniotic fluid,[41] and
- Into the bone marrow (intraosseous).[42]

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[34] Occasionally, some chemotherapy for cancer or infection can be given intrathecally in an attempt to decrease the systemic side effects while maximizing the central nervous system effectiveness, or to compensate for poor passage of many medications across the blood/brain barrier from the blood stream into the cerebrospinal column.

[35] The technique is subdural.

[36] Anti inflammatory steroids, used for severe arthritis, may be injected into the space within a joint. This is called the synovial injections.

[37] The hydration fluids may be given by the slow infusion subcutaneously rather than into a vein. This is called hypodermoclysis, and it is no longer commonly used for large volumes. Small volumes are sometimes given this way. An example of this would be the insulin delivered by a pump.

[38] Intracardiac may be used during the cardiopulmonary resuscitation.

[39] Intratracheal may be used during the cardiopulmonary resuscitation. The medication will be sprayed.

[40] By intra ventricular drugs can be given via catheter into the ventricles of the brain.

[41] During the gestation, the drugs may even be administered to a fetus in utero or into the amniotic fluid (intrauterine injection).

15.5. Drug Dosage Forms

There are diverse numbers of the dosage forms e.g.

- The injections,
- The liquids,
- The pills and powders,
- The rectal dosage,
- The tablets, capsules, and High tech, and
- The topical agents.

15.5.1. Injections

The parenteral dosage forms are mainly the water-based solutions. Further, a few novel approaches are solutions in the solvents other than the water, the oil-in-water emulsions, and even the drug-impregnated solids used as the sub-dermal implants. Recently, the drugs have been delivered inside the liposome in a parenteral liquid.

15.5.2. Liquids

The oral liquids include the solutions such as the teas (infusions and decoctions), fluid extracts, syrups, drops, and tinctures, as well as the emulsions and powders ready for the reconstitution with the water. All oral liquids are relatively simple in the comparison to the oral liquid nutritional supplements. The supplements are generally the oil-based solutions emulsified within the water-based solutions with some of their ingredients suspended in a colloidal form.

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[42] By Intra osseous the injection is done into the bone marrow of the long bones such as in tibia. This may be useful in the children with poor veins and relatively soft bones.

15.5.3. Pills and Powders

The pills consist of the medication combined with the inactive ingredients to form a gelatinous (doughy) mass. This mass is then divided, rolled into the cylinders on a pill tile, and then cut into the individual pills. The pills are the dried prior to use.

15.5.4. Rectal Dosage Forms

The rectal dosage forms are designed for the absorption in the sigmoid colon and may be the solid dosage forms (suppositories), liquids (enemas), or aerosols (foams). Both local and systemically acting the medications may be given via this route. The haemorrhoid treatments, anti-emetics, laxatives, and antipyretics are all commonly given in these forms.

15.5.5. Tablets, Capsules, and High Tech

A tablet is a mixture of the active substances and binders pressed into a solid. It is prepared from a dry mixture of the active and inactive ingredients (excipients). The excipients include:

- The binders,
- The lubricants,
- The diluents, and
- The colouring agents.

The excipients can be used to aid the process by which a product is manufactured. In general, the active substances may not be easily administered and absorbed by the human body. They need to be put in some appropriate form. The active substance is then dissolved or mixed with an excipient. The excipients are also sometimes used to bulk up the formulations with very potent active ingredients, to allow for the convenient and accurate

dosage. The excipients are considered the inert ingredients, but can occasionally cause difficulty in the individual patients. The lactose is commonly used as diluents. The quantity is usually too small to cause the adverse effects, even in a “lactose intolerant patient”.

The capsules are the other most common oral dosing form. Active ingredients, diluents, and lubricants are put into the hard gelatine shells that are then mated with a second gelatine shell. The liquid medication can also be sealed into a capsular shell. Several variations on the manufacturing the tablets and capsules can result in the delayed or extended medication release into the gastrointestinal tract. The absorption of the drug into the bloodstream and the pharmacological effect of the drug will be affected by this alteration in the release of the medicine. The most advanced oral dosage forms use the semi permeable membranes or laser technology to produce the dosage forms that release the medication into the gastrointestinal tract at a controlled rate. Recently, the rapid dissolving tablets have been developed to deliver the medications into the gastrointestinal tract. The medication is released in the oral cavity but is absorbed at numerous locations in the gastrointestinal tract. This results in a quicker onset of the action. The rapid disintegration is frequently associated with this type of the dosage form. The sublingual and buccal tablets are designed to be rapidly dissolved and absorbed into the systemic circulation via the highly vascular environment of the mouth. They are intended to avoid the first-pass effect of the circulation through the liver. The purpose of the enteric coating is twofold. It provides a protective barrier against the acid environment of the stomach for the acid-labile drugs. The drug is delivered intact to the alkaline environment of the small intestine where it dissolves and is then available for the absorption. The enteric coating also used for the purpose of the protecting the lining of the stomach from

drugs that are the gastric irritants. The destruction of the enteric coating allows the active drug to come in contact with the lining of stomach and may result in the nausea or even haemorrhage.

15.5.6. Topical Agents

The ointments (oil base) may deliver the topical medications. The creams (water-soluble base), gels, and mustards also do so. The shampoos, soaps, solutions, and topical patches may also deliver the medication in a useful manner. The nasal, ophthalmic, and otic (for the ear) solutions and suspensions are available. Aerosols, sprays, nebulized[43] medications, metered dose inhalers, and powders for the inhalation are used to deliver the medication to the respiratory tract. Intra-vaginal suppositories (also called vaginal tablets) creams, douches, and sponges are used to deliver the medications.

15.6. Route of Drug Administration in Clinical Trial

In the clinical trials the choice of the route for the drug administration and the rate of the administration have to be met very carefully. In the Phase-Ia trials the careful monitoring for an adverse reaction or exaggerated response is necessary. Further, in the case of an intravenous administration a slow infusion over several hours has to be more appropriate than a slow bolus over several minutes. The slow administration of the drugs will allow the monitoring for an adverse reaction and if there is clinically indicated, timely discontinuation of the infusion in order to prevent a serious outcome.

[43] A nebulizer is a device used to administer the medication to the subjects in forms of a liquid mist to the airways.

15.7. GMP for Medicinal Products for Human Use

All manufacturers of the medicinal products have to operate an effective quality management of their manufacturing operations. This requires the implementation of a pharmaceutical quality assurance system. The pharmaceutical quality assurance means the sum total of the organized arrangements made with the object of the ensuring that the medicinal products are of the quality required for their intended use. For this purpose the good manufacturing practice (GMP) has been defined. Its primary objectives are:

The production,

- The documentation,
- The personnel,
- The quality control,
- The self inspection, and
- The product recall.

15.7.1. Production

The production of the pharmaceutical products has to be performed and supervised by the competent personnel. Also, all handling of the materials and products, such as the receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distributing has to be done in the accordance with the written procedures or instructions and has to be recorded.

15.7.1.1. Incoming materials

All incoming materials have to be checked to ensure that the consignment corresponds to the order. The damage to the containers and any other problem which might adversely affect the quality of a material have to be investigated,

recorded and reported to the Quality Control Department. Also, the incoming materials and finished products have to be physically or administratively quarantined immediately after the receipt or processing, until they have been released for the use or distribution. All materials and products have to be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit the batch segregation and stock rotation.

15.7.2. Documentation

The detailed documentation serves as a basis for the quality evaluation. The Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations. The records provide a history of each batch of the product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product. The documents have to comply with the relevant parts of the manufacturing and marketing authorisation dossiers. They have to be approved, signed and dated by the appropriate and authorised persons. Further, they have to be regularly reviewed and kept up-to-date. When a document has been revised, the systems have to be operated to prevent the inadvertent use of the superseded documents.

15.7.3. Personnel

At each manufacturing site, the manufacturer has to have the competent and appropriately qualified personnel at his disposal in the sufficient number to achieve the pharmaceutical quality assurance objective. The responsibilities placed on any one individual should not be so extensive as to present any risk to the quality. Also, the personnel in the responsible positions have to have specific duties recorded in the written job descriptions and the adequate

authority to carry out their responsibilities. Further, the manufacturer has to provide training for all the personnel whose duties take them into the production areas or into the control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

15.7.3.1. Key Personnel

The key personnel include at least the head of the Production, and the head of the Quality Control. Normally the key posts have to be occupied by the full-time personnel. Further, the heads of the Production and Quality Control have to be independent from each other.

15.7.3.2. Head of Production

The following responsibilities have generally the head of the Production Department:

- To ensure that the required initial and continuing training of his department personnel carried out and adapted according to need,
- To approve the instructions relating to the production operations,
- To ensure the strict implementation of the instruction related to the production operations,
- To ensure that the production records are evaluated,
- To ensure that the production records are signed by an authorised person before they are sent to the Quality Control Department,
- To ensure that the appropriate validations are done,
- To ensure that the produced products are stored appropriate, and
- To check the maintenance of his department, premises and equipment.

15.7.3.3. Head of Quality Control

The following responsibilities have generally the head of the Quality Control Department:

- To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need,
- To approve or reject the starting materials, packaging materials, and intermediate, bulk and finished products,
- To approve the specifications, sampling instructions, test methods and other Quality Control procedures,
- To evaluate the batch records,
- To ensure that all necessary testing is carried out,
- To approve and monitor any contract analysts,
- To ensure that the appropriate validations are done, and
- To check the maintenance of his department, premises and equipment.

15.7.4. Quality control

The holder of a Manufacturing Authorisation has to manufacture the medicinal products by ensuring that:

- The medicinal products are fit for their intended use,
- The medicinal products comply with the requirements of the Marketing Authorisation,
- The medicinal products do not place the subjects at the risk due to
  - The inadequate safety,
  - The inadequate quality, or
  - Inadequate efficacy.

The attainment of this quality objective is the responsibility of the senior management and requires the participation and commitment by the staff in

many different departments and at all levels within the company. Also, the senior management has to establish and maintain a quality control department. This department has to be placed under the authority of a person having the required qualifications. Further, this person has to be independent of the other departments.

15.7.5. Self inspection

The manufacturer has to conduct the repeated self-inspections as part of the quality assurance system in order:

- To monitor the implementation and respect of the good manufacturing practice, and
- To take any necessary corrective measures.

15.7.6. Product recall

The procedures for the retrieving IMP, and the documenting this retrieval should be agreed by the sponsor, in the collaboration with the manufacturer or importer. The investigator and monitor need to understand their obligations under the retrieval procedure. Also, the sponsor has to ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for the communication to the sponsor for the need of recall any product supplied.

In the case of the returns, the IMP has to be returned on the agreed conditions defined by the sponsor, and specified in the approved written procedures. Also, the returned IMP has to be clearly identified and stored in an appropriately controlled and dedicated area.

15.8. Imported Medical Products

For the importing medicinal products from the third countries into the EU Member State the authorisation is required. The competent authorities issue the authorisation only after the verifying the accuracy of the application. The competent authorities complete all appropriate measures to ensure that the procedure for the granting an authorisation within 90 days of the day on which the competent authority receives a valid application.

The importer has to ensure that the medicinal products have been manufactured by the manufacturers duly authorized and conforming to the GMP standards, at least equivalent to those laid down by the Community. Also, all appropriate measures have to be taken to ensure that the manufacture or the importation of the IMP is the subject to the holding of the authorisation. In order to obtain the authorisation, the applicant and, subsequently, the holder of the authorisation, have to meet at least the defined requirements. The holder of the authorisation has to fulfil following requirements:

- One qualified person is permanently and continuously at his disposal.
- Each batch of the IMP has been manufactured and checked in compliance with the requirements of the principles and guidelines of the GMP for the medicinal products for the human use.
- In the case of the manufacturing in a third country each production batch has been manufactured:
  - In accordance with the standards of the GMP,
  - In accordance with the product specification file, and
  - Each production batch has to be checked.
- Each production batch has to undergo all relevant analyses, tests or checks necessary to confirm its quality.

- The qualified person has to certify in a register or equivalent document that each production batch satisfies the provisions.
- The register or equivalent document has to be kept up to date as the operations are carried out.
- The register or equivalent document has to remain at the disposal of the agents of the competent authority for specified period which is at least five years.

The competent authority can suspend or revoke the authorisation, as a whole or in part, if the holder of the authorisation fails at any time to comply with the relevant requirements.

15.9. Labelling

The labelling of the IMP is complex, and liable to the errors than the labelling for the marketed products, particularly when the "blinded" products with similar appearance are used. The labels have to appear in at least the official language on the outer packaging of the IMP or, where there is no outer packaging, on the immediate packaging. Also, the labels for the IMP have to have the following characters:

- The name, address and telephone number of the sponsor, CRO, or investigator,
- The pharmaceutical properties,
  - The dosage form,
  - The route of the administration,
  - The quantity of the dosage units, and
  - In the case of the open trials, the name/identifier and strength/potency,
- The batch and/or code number to identify the contents and packaging operation,

- A trial reference code allowing,
  - The identification of the trial,
  - The identification of the site,
  - The identification of the investigator, and
  - The identification of the sponsor,
- The trial subject identification number,
- The treatment number or the visit number,
- The directions for the use “For clinical trial use only”,
- The storage conditions,
- The period of use, and
- To keep out of reach of the children.

16. Source data

The source data are contained in the source documents. Also, the source data can be available as the electronic data, or as the hard copies. According to the ICH-GCP (1.51) the source data are:

- All information in the original records,
- The certified copies of the original records of the clinical findings, and
- The observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

16.1. Electronic data

The Electronic Data Management Systems are very common for collecting the patient source data in both the inpatient and outpatient setting. They have to be secure and valid. Also, in order to ensure that the quality of the data within the electronic systems meets the relevant regulations and the ICH-GCP requirements, the source documents for the patient at each investigational site should be identified and any electronic systems involved has to be assessed for the quality assurance. It is important that the quality of the data collected electronically is as robust as that collected on the paper. Also, the Electronic Data Management System has to full fill at least the following points:

- The access control (through Password Management),
- The data change control (Audit Trail),
- The physical security,
- The systems back-up, and
- The archiving procedures.

16.1.1. Access Control and Password Management

Access control means that the adequate safeguards are in place to protect the integrity and confidentiality of the patient data in the computer system.

- The computer access is restricted and limited to the authorized personnel.
- There is an automatic locking of the system activated when the system is not in the use.
- The data access is only restricted and limited to the authorized personnel.
- There is a current record that indicates the names of the authorized personnel, and their access privileges.

16.1.2. Physical security

Physical security of the electronic systems for the data entry or data capture at the investigational sites is of great importance. In assessing the physical security the system has to have the following properties:

- In a secure and locked location with the restricted access,
- Adequate protection from the risks, such as the fire, and flooding,
- Vendor support for the hardware replacement,
- Adequate safeguards for the virus protection, and
- Adequate protection from the corruption or damage due to the viruses.

16.1.3. Audit Trail

Audit trails are important within a system in order to the unambiguously record:

- Who made changes to which data?
- Which data has been changed?
- At which time the changes have been occurred?

16.1.4. System Back-up

Back-up for the electronic data is very important. It is necessary to be able to generate the accurate and complete copies of the records in both the normal (human readable) and electronic format. The following points have to be considered for the back-up of the electronic data:

- Who is responsible for the back-up?
- Who is the owner of the data?
- Which data are backed up?
- What is the frequency of the back-up?
- What media is used for the back-up (e.g. CD-ROM, disk)?
- On which place the back-up media will be stored (in-house/fire proof; external/off-site)?
- In the event of a system failure are there the contingency plans for how the data would be collected or stored?

16.1.5. Archiving Procedures

The electronic systems need to ensure the compliance with the ICH-GCP and the FDA regulations for the archiving of the clinical trial documents. The current standard for the archiving is 15 years. For the accurate archiving the following points have to be considered:

- The storage of all electronic records,
- The documentation of what the electronic records have been stored, and
- The documentation of where the electronic records are located.

16.2. Source Document Requirements

According to the ICH-GCP guidelines the monitoring team has to check the CRF entries against the source documents, except for the pre identified source data directly recorded in the CRF.

17. Insurance Coverage for Clinical Trial

A sponsor of a clinical trial on the therapeutic products has to compensate a trial subject for any damage that he or she may suffer within the framework of the clinical trial. Also, the trial sponsor needs the liability insurance to carry the clinical trial. The requirement makes sense because most countries provide the public health services. While states involved in performing the clinical trials doesn't want to be stuck with the bill in the event the subjects are injured by an IMP or the sponsor goes out of the business. Also, the clinical trials require the unique coverage to provide the maximum insurance protection. The sponsor needs to purchase the additional liability insurance specifically designed to cover the clinical trials. The clinical trials insurance is a highly specialized product. The sponsors have to provide a copy of the insurance certificate to the EC/IRB. The provisions for the indemnity or compensation in the case of the injury or death of a trial subject have to be described to the EC/IRB. There has to be the arrangements to cover the liability of the sponsor and investigator.

17.1. Insurance Compensation

The sponsor has to certify that it has taken out a liability insurance policy which covers the liability of the investigator. This insurance policy has to be in accordance with the local laws and requirements.

17.2. Object of Insurance Policy

The insurance company offers the insurance coverage in the event that during a clinical trial carried out, any trial subjects involved are killed, physically injured, or suffer harm to their health (personal damages) or that any trial subjects suffer the material damage in relation to the clinical trial. Also, the

insurance coverage is intended for the personal damages suffered by a trial subject in relation to a clinical trial. The insurance coverage also extends to claims for the personal damages caused by the procedures carried out on the trial subject in relation to the clinical trial on the therapeutic product.

17.3. Obligations of Trial Subject

For the duration of the clinical trial, the trial subject has to inform the investigator immediately or at the next visit about any other illnesses or complaints that have arisen in the meantime and about any medication taken for such illnesses or complaints. In these cases the investigator has to report any personal damages that may have occurred as a consequence of the clinical trial without delay to the sponsor.

17.4. Restrictions to Scope of Insurance Policy

There are some restrictions for the insurance coverage. Normally it does not extend to claims of the following nature e.g.:

- The damages and a deterioration of the existing state of the health which would have occurred or persisted even without participation in the clinical trial,
- The damages that occurred because the trial subject contravened the express instructions of the investigator or written instructions given in the informed consent,
- The compensation for the "punitive damages",
- The damages arising from the substances/formulations or preparations listed in the informed consent form,
- The damages to a trial subject in the control group,

- The damages to a trial subject that do not exceed a certain degree of the adverse reactions that are to be expected from the trial drug according to the current state of the medical knowledge, and
- The damages to a trial subject that do not exceed a certain degree of the adverse reactions that is to be expected from the trial drug according to the current state of the medical knowledge.

18. Identification Number for Clinical Trial

In Europe before starting the clinical trial each trial will receive a uniquely identifiable number. The product (and active substance) names has to be clearly traceable and identifiable throughout its development and has to be used in the different clinical trials, and through to post marketing for those products, which are or become available on the market. Where a product that is being used in the trial has a marketing authorisation in the community the trade name and the marketing authorisation number need to be provided, in addition to the name of the active ingredient. The information entered should be complete for each trial and therefore a response to each element is mandatory. For each study the sponsor provides the data required in electronic format, prior to or at the time of the application to the competent authority. The EudraCT Database is a register of:

- All clinical trials in the community,
- The information on the content,
- The commencement and termination of the clinical trials, and
- On the inspections.

The unique EudraCT number for each clinical trial has the format YYYY-NNNNNN-CC, where:

- YYYY is the year in which the number is issued,
- NNNNNN is a six digit sequential number, and
- CC is a check digit.

The EudraCT Database has:

- To provide an overview of the clinical trials being conducted in the community,

- To facilitate the communication on these clinical trials between the authorities,
- To enable each authority to undertake the better oversight of the clinical trials and the IMP development,
- To provide enhanced protection of the clinical trial subjects and patients receiving the IMP, and
- To be interfaced with the EudraVigilance Clinical Trial Module. The EudraCT database and the EudraVigilance Clinical Trial module share the common key fields including the clinical trial identification, the product identification and the sponsor identification.

The users of the EudraCT database are:

- The competent authorities of the Member States,
- The Agency, and
- The Commission of the European Union.

It is, in addition, designed to be linked with the European database of the reports of the SUSAR's reported during the clinical trials for the IMP.

The EuraCT Database will purpose:

- The provision of an overview of all clinical trials in the community,
- The facilitation of the communication between the Member States, the Agency and the Commission on the clinical trials,
- The identification of the ongoing, completed or terminated clinical trials, conducted at one or more sites in the community, e.g.:
  - With a given product,
  - Conducted by a given sponsor,
  - By the patient population,
  - By the product type,

- By the indication/disease under the investigation/therapeutic area, and
- The generation of the clinical trial statistics,

➢ The identification of the clinical trials, sponsors and IMP involved in order to support the interface between the clinical trial information (in EudraCT) and reports of the SUSAR's (in the EudraVigilance Clinical Trial Module),

➢ The provision of the information on the ICH-GCP and the clinical trial related GMP inspections that have been undertaken by the competent authorities Inspectorates e.g.:

- For a given product,
- For a given clinical trial,
- For a given sponsor, and
- For specified clinical trial sites,

➢ The system inspections of the sponsor/CRO/laboratory/clinical facilities etc., and

➢ The notification to all competent authorities when a trial is terminated for the safety reasons.

18.1.1. EudraCT Number

One EudraCT number will be issued per protocol, irrespective of the number of the clinical trial sites or member states involved. Also, a EudraCT number will only be issued once by the system. If a number is issued but the clinical trial does not proceed number is not available for reuse. The EudraCT number is issued to the sponsor by a central function in the system on the submission of the required data to the system. It has to be included:

➢ In the submission of the request for the trial to the competent authorities,

➢ In the submission of the request for the trial to the EC/IRB,

➢ On any amendments,

- On the end of the trial report, and
- On the SUSAR for the reports from the trials.

The sponsor's protocol code number and the amendment code numbers has to be included in the database. Where an International Standard Randomised Controlled Trial Number (ISRCTN) is available for the trial, this has to be entered.

18.1.2. Quarantine Area

The sponsor submits the data required in the electronic format to a Quarantine Area, from which the competent authority enters it into the EudraCT database, by the electronic transfer, and after a confirmation check of the data. The Quarantine Area is accessible:

- To the competent authorities of the Member States,
- To the Agency, and
- To the Commission.

Each sponsor can only access their own data in the Quarantine Area. The Quarantine Area will contain a separate location in which each sponsor can prepare and draft their forms before submitting them and in which they can maintain an updated version of the data if they choose during the course of the trial and afterwards. The sponsor receives an updated file of the data submitted when it has been entered into the EudraCT database by the competent authority. This permits the sponsor to maintain a current version in their secure area.

18.1.3. User for System

Each sponsor registers the single or multiple users with the system. The sponsor can delegate the task of submitting the information to the system, to other parties, so the sponsor can register the representatives/authorised parties to act on its behalf but the sponsor retains the ultimate responsibility for the submitted data. The first part provides the facilities for obtaining a EudraCT Number for a Clinical Trial Application. This is a two-step process:

- A security code reference will be obtained as a means of the validating the EudraCT Number request, and
- Some simple information about the requestor and the Sponsor's Protocol Code Number of the trial for which the EudraCT number is required.

There are two simple forms to collect the information required and the security code and EudraCT number will be returned by the e-mail. The EudraCT number is used as the unique reference to a clinical trial on the clinical trial application form. The second, major part of the EudraCT system is based on a set of the web pages that will collect the information required to complete the clinical trial application, save the data to disc, print paper copies for the Member State Competent Authorities (MSCA) and EC/IRB and then make an electronic copy for despatch to the MSCA. There are also facilities to download the forms for "The Request for Authorisation of a Substantial Amendment to a Clinical Trial" and for the "Declaration of the End of a Clinical Trial".

The system is based on the web enabled request forms. These collect the information required for the request of a security code, the EudraCT Number and the data required for clinical trial application form. The system has been designed to be as flexible as possible in order to meet the varying

requirements of each Member State. For this reason there are very few mandatory data items, so it is necessary for all users to carefully check the clinical trial application forms for the data consistency.
To operate the EudraCT system the sponsor needs to have a current e-mail account and software on his/her PC that enables him/her to receive the e-mails.
http://www.emea.eu.int

18.1.4. Availability of EudraCT number

The sponsor can obtain the EudraCT number for inclusion on the internal documentation and other planning by the completion of the minimum set of the parameters (essentially sponsor, protocol and test product information). The remaining data required for the trial has to be completed then or later but has to be complete by the time of the submission of the request for the authorisation of the trial to the competent authorities.

18.1.5. Submission of Information

Unless the clinical trial is registered in the database before the trial starts, it will not be possible to ensure that the trial and the product to which each SUSAR relates is clearly identified and traceable, nor it will be possible to register the amendments. Therefore all the information required from the sponsor for the database, applicable to a given trial and available at the time of the submission of the request to the competent authority, has also to have been submitted, in the electronic format, by the sponsor to the Quarantine Area, by that time. If the sponsor realises that an error, or omission has been made in the data submitted, or the information has changed prior to the submission to the competent authority, the sponsor can log-on, with access only to their own

submitted information, and correct this, until such time as the data is entered into the EudraCT from the Quarantine Area by the competent authority.

To simplify the process of the application by the sponsors to the competent authorities and the EC/IRB, the system facilitates the preparation of the complete paper submission forms to both. The submission forms to the competent authorities of the Member States and the submission forms to the EC/IRB are available from the system, which will enable the generation of these forms with the questions and headings in the official languages of the Member States.

18.1.6. Competent Authority and EudraCT

Upon receipt of the electronic data submitted by the sponsor, the competent authority will perform an administrative confirmation of the data, by the comparison with the full submission form accompanying the request for the clinical trial. This confirmation is an administrative check that

- The fields are complete and contain the information appropriate to the fields, and
- That the information is in accordance with that supplied on the form accompanying the full paper submission.

The competent authority then takes the data electronically from the Quarantine Area and enters this data into the EudraCT database. The competent authority performs this transfer at day 0 following the validation. For the single state trials, the competent authority of the concerned Member State will do this.

For the multi-state trials the data will be entered by the first Member State acting on the dossier, each other Member State, on receipt of the application,

confirms the common data and enters the data specific to its territory. In case of an inaccuracy or omission the authority queries it with the sponsor if they consider. If the data is specific to the Member State, any correction is made by the Member State generating the query, or by the sponsor. If the data correction/update also relates to the study conduct in the Member States where the review of the dossier has already commenced the sponsor will need to make an amendment.

18.1.7. Change of Submitted Data

If the information contained in the initial submission (application form, protocol or other documentation) of a clinical trial changes significantly, then this has to be notified to the competent authority as an amendment. The sponsor completes the required information in the amendment screens of the Quarantine Area. The sponsor completes the amendment form and sends this with the supporting documentation as required to the competent authority. On receipt of the forms the competent authority verifies the data as for an initial submission and then updates those fields that have changed, by entering the sponsor supplied amending information from the Quarantine Area into the EudraCT database. This process results in an update of the locked file of the sponsor information in the Quarantine Area, thus ensuring that the sponsor has available a copy of an up to date version of the information they supplied to the competent authorities.

18.1.8. Data Quality Assurance and Quality Control

It is the responsibility of the party making the data submission or entry, to ensure the accuracy and completeness of the data at the time it is first entered. The sponsor is responsible for the accuracy of the submitted data to the

competent authorities. The competent authority is responsible for the data entered into the database, based on that submitted by the sponsor.

18.1.9. Response of Competent Authority to EudraCT-Database

The response of the competent authorities displaying the EudraCT number has to be:

- Submitted to the EC/IRB,
- The EudraCT number has to be used on any amendments and on the end of the trial report, and
- The EudraCT number has also to be used on the SURAR reports for the reports from the trials with the sites.

18.1.10. Sponsor Registration with System

It is necessary that the sponsors register with the system prior to using it for any purpose. The registration serves two key purposes:

- The security for protecting the system from the unauthorised access, and
- Authenticity of the submitted information.

Once the registration has been completed the sponsor obtains the EurdaCT number which makes it possible to provide the data, and have access to the submitted data.

19. Regulatory and Ethical Issues

For conducting the clinical trials the following ethical and regulatory guidelines have to be followed:

- Declaration of Helsinki,
- ICH, and
- GCP.

19.1. Declaration of Helsinki

The Declaration of Helsinki has been developed by the World Medical Association. It is a set of the ethical principles for the medical community regarding the experiments on the humans. It was originally adopted in June 1964 and has since been amended multiple times. In 1975 the Declaration countenanced the minors as the research subjects. The principle 11 stated, "When the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. The possibility of a minor being able to give consent was incorporated into the 1983 revision of the Declaration: "The minor's consent must be obtained in addition to the consent of the minor's legal guardian". The Declaration was further revised in 2000, in Edinburgh, Scotland.

The Declaration considers the conduct of the clinical trial. Like the Nuremberg Code, the Declaration made the informed consent as a central requirement for the ethical research while allowing for the surrogate consent when the research participant is incompetent, physically or mentally incapable of giving the consent. The Declaration urged that in the clinical research combined with the professional care then the consent has to be obtained, "if at all possible". It was only in the section on the "Non-therapeutic clinical research" that the issue

of the consent was given prominence, but only as the third principle. According to the Declaration in the cases when the subject is legally incompetent but able to give assent to the decisions about the participation in the research, assent has to be obtained in addition to the consent of the legally authorized representative.

The History of the Declaration of Helsinki

Jun. 1964	Adopted by the 18th WMA General Assembly Helsinki, Finland
Oct. 1975	amended by the 29th WMA General Assembly, Tokyo, Japan
Oct. 1983	35th WMA General Assembly, Venice, Italy
Sep.1989	41st WMA General Assembly, Hong Kong
Oct. 1996	48th WMA General Assembly, Somerset West, Republic of South Africa
Oct. 2000	52nd WMA General Assembly, Edinburgh, Scotland
2002	Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington
2004	Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo

The Declaration of Helsinki contains three parts:

Part A. Introduction

Part B Basic principles for all medical research

Part C Additional principles for medical research combined with medical care

19.1.1. Introduction

The introduction of the Declaration of Helsinki contains nine points:

1. The World Medical Association has developed the Declaration of Helsinki as a statement of the ethical principles to provide guidance to the physicians and other participants in the medical research involving the human subjects.

The medical research involving the human subjects includes the research on the identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on the research which ultimately must rest in part on the experimentation involving the human subjects.

5. In the medical research on the human subjects, the considerations related to the well-being of the human subject should take precedence over the interests of the science and society.

6. The primary purpose of the medical research involving the human subjects is to improve the prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of the disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through the research for their effectiveness, efficiency, accessibility and quality.

7. In the current medical practice and in the medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. The medical research is the subject to the ethical standards that promote respect for all human beings and protect their health and rights. Some research

populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be the subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. The research Investigators should be aware of the ethical, legal and regulatory requirements for the research on the human subjects in their own countries as well as the applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for the human subjects set forth in this Declaration.

19.1.2. Basic Principles for all Medical Research

"Basic principles for all medical research" of the Declaration of Helsinki contains 18 points (number 10 to 27):

1. It is the duty of the physician in the medical research to protect the life, health, privacy, and dignity of the human subject.
2. The medical research involving the human subjects must conform to the generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of the information, and on the adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of the research which may affect the environment, and the welfare of the animals used for the research must be respected.
4. The design and performance of each experimental procedure involving the human subjects should be clearly formulated in an experimental protocol. This

protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor the ongoing trials. The researcher has the obligation to provide the monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding the funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for the subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. The medical research involving the human subjects should be conducted only by the scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving the human subjects should be preceded by careful assessment of the predictable risks and burdens in comparison with the foreseeable benefits to the subject or to others. This does not preclude the participation of the healthy volunteers in the medical research. The design of all studies should be publicly available.

8. The physicians should abstain from engaging in the research projects involving the human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. The

physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. The medical research involving the human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. The medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of the research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on the human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from the participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving the consent or is a legally incompetent minor, the investigator must obtain the informed consent from the legally authorized representative in accordance with the applicable law. These groups should not be included in the research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on the legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about the participation in the research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. The research on the individuals from whom it is not possible to obtain consent, including the proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining the informed consent is a necessary characteristic of the research population. The specific reasons for involving the research subjects with a condition that renders them unable to give the informed consent should be stated in the experimental protocol for the consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both the authors and publishers have the ethical obligations. In the publication of the results of the research, the investigators are obliged to

preserve the accuracy of the results. The negative as well as positive results should be published or otherwise publicly available. The sources of the funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. The reports of the experimentation not in accordance with the principles laid down in this Declaration should not be accepted for the publication.

19.1.3. Additional Principles for Medical Research

"Additional principles for medical research combined with medical care" of the Declaration of Helsinki contains 5 points (number 28 to 32):

1. The physician may combine the medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When the medical research is combined with the medical care, additional standards apply to protect the patients who are the research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of the placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with the informed consent from the patient, must be free to use the unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving the life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of the research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published.
http://www.wma.net/e/policy/b3.htm

19.2. ICH

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the USA and the experts from the pharmaceutical industry. In the 1980s the European Union moved towards the development of a single market for the pharmaceuticals. Also, the harmonisation of the regulatory requirements was required. The success achieved in Europe demonstrated that the harmonisation was feasible. At the WHO Conference of the Drug Regulatory Authorities in Paris in 1989 the specific plans for action began to materialise. Soon afterwards, the authorities approached the IFPMA[44] to discuss a joint regulatory-industry initiative on the international harmonisation, and the ICH was conceived. In April 1990 representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International

[44] The International Federation of Pharmaceutical Manufacturers & Associations

Conference but the meeting also discussed the wider implications and terms of the reference of the ICH.

The ICH is comprised of the Six Parties which are directly involved, as well as three Observers[45] and the IFPMA. The Six Parties are the founder members of the ICH. They represent the regulatory bodies, and the research-based industry in the EU, Japan and the USA. These parties include the EU, EFPIA[46], MHLW[47], JPMA[48], FDA, and PHRMA[49].

The ICH Steering Committee will meet at least twice a year, with the location rotating between the three regions Europe, Japan and the USA. The first priority that the Steering Committee has given was the harmonising the technical content of the sections of the reporting data where significant differences have been identified between the regulatory requirements across the three regions. Also, the first ICH Guideline was the harmonisation the format of the reporting data, and the content and format of the Clinical Study Reports. This Guideline describes a single format for reporting the core clinical studies that make up the clinical section of a registration dossier. The ICH process has achieved success:

- Based on the scientific consensus developed between the industry and regulatory experts, and

[45] The ICH Observers are: WHO, EFTA (European Free Trade Association), and Canada.

[46] The EFPIA (European Federation of Pharmaceutical Industries and Associations) is situated in Brussels. It members are 29 national pharmaceutical industry associations, and 45 leading pharmaceutical companies involved in the research, development and manufacturing of the medicinal products in Europe for the human use.

[47] The MHLW (Ministry of Health, Labour and Welfare, Japan) has responsibilities for the approval, and administration of the drugs, medical devices and cosmetics in Japan.

[48] The JPMA (Japan Pharmaceutical Manufacturers Association) represents 75 members (all the major research-based pharmaceutical manufacturers in Japan), and 14 committees.

[49] The PhRMA (Pharmaceutical Research and Manufacturers of America) represents the research-based industry in the USA. It contains 67 companies that are involved in the discovery, development and manufacture of the prescription medicines. There are also 24 research affiliates which conduct biological research related to the development of the drugs and vaccines.

- Based on the commitment of the regulatory parties to implement the ICH tripartite, harmonised guidelines and recommendations.

The History of the ICH

Nov. 1991	First International Conference on Harmonisation, Brussels, Belgium
Oct. 1993	Second International Conference on Harmonisation, Orlando, USA
Nov. 1995	Third International Conference on Harmonisation, Yokohama, Japan
Jul. 1997	Fourth International Conference on Harmonisation, Brussels, Belgium
Nov. 2000	Fifth International Conference on Harmonisation, San Diego, USA
Nov. 2003	Sixth International Conference on Harmonisation, Osaka, Japan

The goal of the revised ICH terms of the reference (revised in 1997) is:

- Maintaining a forum for a constructive dialogue between the regulatory authorities and the pharmaceutical industry,
- Contributing to the protection of the public health from an international perspective,
- Monitoring and update the harmonised technical requirements leading to a greater mutual acceptance of the research and development data,
- Avoiding the divergent future requirements through the harmonisation of the selected topics which are needed as a result of the therapeutic advances, and the development of new technologies for the production of medicinal products,

- Facilitating the adoption of the new or improved technical research and development approaches which update or replace the current practices,
- Facilitating the dissemination of the information on the harmonised guidelines and their use such as to encourage the implementation and integration of the common standards, and
- Facilitating the communication of the information on the harmonised guidelines and their use such as to encourage the implementation and integration of the common standards.

http://www.ich.org/cache/compo/276-254-1.html

19.2.1. Development of Safety Update Report

While the recent implementation of the EU Clinical Trial Directive the need for the global harmonization of the annual safety reporting for the developmental programs has accelerated the harmonization is necessary to stem the emergence of the technical variations across the different regulatory jurisdictions. Also, the ICH is developing a guideline on the periodic reporting of the safety information from the clinical trials. This guideline is defining the preferred content, format, and timing of such reports. This type of the report will be called the Development Safety Update Report (DSUR). By using the DSUR the industry will regularly inform the appropriate stakeholders of the new safety data and the evolving safety profile of the drugs, vaccines, and therapeutic biologic products before they are marketed. The objective of the proposed DSUR for the clinical trials is similar to that of the Periodic Safety Update Report (PSUR) that is commonly used for the marketed pharmaceutical products.

19.3. Good Clinical Practice (GCP)

The Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the designing, conducting, recording and reporting the trials that involve the participation of the human subjects. The compliance with this standard provides the public assurance that the rights, safety and well-being of the trial subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

- Providing a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of the clinical data by the regulatory authorities in these jurisdictions.
- Development with the consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).
- Follow when generating the clinical trial data are intended to be submitted to the regulatory authorities.
- The principles established in this guideline have also to be applied to other clinical investigations that may have an impact on the safety and well-being of the human subjects.

All clinical trials, including the bioavailability and bioequivalence studies, have to be designed, conducted and reported in accordance with the principles of the GCP. The GCP is a set of the internationally recognised ethical and scientific quality requirements which has to be observed for the designing, conducting, recording and reporting the clinical trials that involve the participation of the human subjects. Compliance with this good practice

provides assurance that the rights, safety and well-being of the trial subjects are protected, and that the results of the clinical trials are credible. The principles of the GCP and detailed guidelines in line with those principles have to be adopted and, if necessary, revised to take account of the technical and scientific progress.

Any investigation in the human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more IMP, and/or to identify any adverse reactions to one or more IMP and/or to study the absorption, distribution, metabolism and excretion of one or more IMP with the object of ascertaining its safety and/or efficacy. Following the GCP Guidelines provides reassurance

- That the rights, safety and well being of the trial subjects are protected through,
  - The review and approval of the study by the EC/IRB, and
  - The signing the informed consent by the patients,
- That the collected data are credible,
  - The source documents, and
  - The Case Report Form, and
- That the trial has been conducted in accordance to the study protocol.

19.3.1. Investigator

Due to the ICH-E6 the investigator is a person who is responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of the individuals at a trial site, the investigator is the responsible leader of the team and has to be called the principal investigator. The investigator has the following responsibilities:

- The Investigator's Qualifications and Agreements

- Qualified by the education, training, and experience to assume the responsibility for the proper conduct of the trial.
- Qualified as specified by the applicable regulatory requirement.
- Evidence of the qualifications through the up-to-date curriculum vitae.
- Familiar with the appropriate use of the investigational product.

➢ The Adequate Resources.

- Potential for recruiting the required number of the suitable subjects within the agreed recruitment period.
- Sufficient time to properly conduct and complete the trial within the agreed trial period.

➢ The Medical Care of the Trial Subjects

- A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- Ensuring the adequate medical care to a subject for any adverse events, including the clinically significant laboratory values, related to the trial.
- Informing a subject when the medical care is needed for the inter-current illness of which the investigator becomes aware.

➢ The Communication with the EC/IRB

- Approval/favourable opinion from the EC/IRB for the trial documents before initiating a trial.
- Providing the EC/IRB all documents subject to review.

➢ The Compliance with the Study Protocol

- Conducting the trial in compliance with the approved study protocol.
- The implementation of any deviation from, or changes of the protocol with the agreement by the sponsor and after the approval/favourable opinion from

the EC/IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects.

- The Investigational Product
  - The responsibility for the investigational product accountability at the trial site.
  - Providing the doses specified by the protocol and reconciled all investigational product received from the sponsor.
- The Randomization Procedures and Unblinding
  - Following the trial's randomization procedures.
  - The documentation and explanation of any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s) to the sponsor.
- The Informed Consent of the Trial Subjects
  - Obtaining and documenting the informed consent.
- The Records and Reports
  - Ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF and in all required reports.
- The Progress Reports
  - Submission of the written summaries of the trial status to the EC/IRB.
- The Safety Reporting
  - Reporting immediately to the sponsor by the detailed, written reports.

19.3.2. EC/IRB

Due to the ICH-E6 the EC/IRB is an independent body constituted of the medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the human subjects involved in a trial by, among other things, reviewing, approving, and

providing continuing review of the trial protocol and amendments and of the methods and material to be used in obtaining and documenting the informed consent of the trial subjects.

The Responsibilities

- Safeguarding the rights, safety, and well-being of all trial subjects.
- Paying the special attention to the trials that may include the vulnerable subjects.
- Obtaining the following documents for approval:
  - The trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates,
  - The IB,
  - The available safety information,
  - The information about the payments and compensation available to the subjects,
  - The investigators current curriculum vitae and/or other documentation evidencing the qualifications, and any other documents that the EC/IRB may need to fulfil its responsibilities.
- Reviewing a proposed clinical trial within a reasonable time and document.
- The documentation of its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:
  - The approval/favourable opinion,
  - The modification required prior to its approval/favourable opinion,
  - The disapproval / negative opinion, and
  - The termination/suspension of any prior approval/favourable opinion.

- Considering the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the EC/IRB requests.
- The continuing review of each ongoing trial at intervals appropriate to the degree of the risk to the human subjects, but at least once per year.
- Reviewing both the amount and method of the payment to the subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.
- Ensuring that the information regarding the payment to the subjects, including the methods, the amounts, and the schedule of the payment to the trial subjects.

➢ The Composition, Functions and Operations

- Consist of a reasonable number of the members:
  - At least five members,
  - At least one member whose primary area of interest is in a non-scientific area, and
  - At least one member who is independent of the institution/trial site.
- Performing its functions according to the written operating procedures.
- Making the decisions at the announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.
- Only members who participate in the EC/IRB review and discussion should vote/provide their opinion and/or advice.
- The investigator may provide the information on any aspect of the trial, but should not participate in the deliberations of the EC/IRB or in the vote/opinion of the EC/IRB.
- Inviting the non-members with the expertise in the special areas for assistance.

- The Procedures

19.3.3. Monitor

Due to the ICH-E6 the monitor oversee the progress of a clinical trial, and ensure that it is conducted, recorded, and reported in accordance with the protocol, the SOPs, the GCP, and the applicable regulatory requirement. They will be appointed by the sponsor. The monitors should be appropriately trained, and have the scientific and/or clinical knowledge needed to monitor the trial adequately. The monitor has the following responsibilities:

- Ensuring that the trial is conducted in accordance with the sponsors requirements
- Carrying out the following activities when relevant and necessary to the trial and the trial site:
  - Acting as the main line of the communication between the sponsor and the investigator
  - Verifying that the investigator has the adequate qualifications and resources,
  - Verifying for the investigational product:
    - The acceptable storage times and conditions.
    - Supplying the investigational product only to the subjects who are eligible to receive it and at the protocol specified dose.
    - Providing the subjects with the necessary instruction on properly using, handling, storing, and returning the investigational product.
    - The adequately documentation of the receipt, use, and return of the investigational product at the trial sites.
    - The disposition of the unused investigational product at the trial sites comply with the applicable regulatory requirement.

- Verifying that the investigator follows the approved protocol and all approved amendment, if any.
- Verifying that the written informed consent was obtained before each subject's participation in the trial.
- Ensuring that the investigator receives the current IB, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement.
- Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

➢ The Monitoring Procedures

o Following the sponsors established written SOPs

o Following those procedures that are specified by the sponsor for monitoring a specific trial.

➢ The Monitoring Report

o Submission of a written report to the sponsor after each trial-site visit or trial-related communication.

o The submitted reports should include:

- The date, site, and name of the investigator or other individual contacted.
- Name of the monitor.
- A summary of what the monitor reviewed.
- The monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

o The documentation and review of the monitoring report, and follow-up by the sponsors designated representative.

19.3.4. Sponsor

Due to the ICH-E6 the sponsor is an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. The sponsor has the following responsibilities:

- The Quality Assurance and Quality Control
  - The implementation and maintaining the quality assurance and quality control systems with the written SOPs to ensure that,
    - The trials are conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
    - The data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- Ensuring the direct access to all trial related sites, source data/documents, and reports from all involved parties for the purpose of the monitoring and auditing by the sponsor, and the inspection by the domestic and foreign regulatory authorities.
- Ensuring the quality control to each stage of the data handling that all data are reliable and have been processed correctly.
- The written agreements with the investigator/institution and any other parties involved with the clinical trial as part of the protocol or in a separate agreement.
- The Contract Research Organization (CRO)
  - Transferring any or all of the sponsor's trial-related duties and functions to a CRO.
    - The ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

- The implementation of the quality assurance and quality control by the CRO.

o The written specification of any transferred and assumed the trial-related duty and function by a CRO.

o Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

➢ The Medical Expertise

o The designation of the appropriately qualified medical personnel who will be readily available to advising on the trial related medical questions or problems.

➢ The Trial Design

o Utilizing the qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from

- The designing the protocol and CRF.
- Planning the analyses to analyzing.
- Preparing the interim and final clinical trial reports.

o Following the ICH Guideline for the Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on the trial design, protocol and conduct.

➢ The Trial Management, Data Handling, and Record Keeping

➢ The Investigator Selection

➢ The Allocation of the Responsibilities

➢ The Compensation to the Subjects and Investigators

➢ The Financing

➢ The Notification/Submission to the Regulatory Authority

➢ The Confirmation of Review by the EC/IRB

- The Information on the Investigational Product
- Supplying and Handling the Investigational Product

o Supplying the investigator(s)/institution(s) with the investigational product.

o Supplying an investigator/institution with the investigational product after the sponsor obtains all required documentation (e.g. approval/favourable opinion from the EC/IRB and regulatory authority).

o Ensuring that the written procedures include the instructions that the investigator/institution should follow for the handling and storage of the investigational product for the trial and documentation thereof.

o Ensuring timely delivery of the investigational product to the investigator.

o Maintaining the records that document the shipment, receipt, disposition, return, and destruction of the investigational product.

o Maintaining a system for retrieving the investigational products and documenting this retrieval (e.g. for the deficient product recall, reclaim after the trial completion, expired product reclaim).

o Maintaining a system for the disposition of the unused investigational product and for the documentation of this disposition.

o Ensuring that the investigational product is stable over the period of use.

o Maintaining the sufficient quantities of the investigational product used in the trials to reconfirm specifications, should this become necessary, and maintain records of the batch sample analyses and characteristics.

- The Record Access
- The Safety Information

o Responsible for the ongoing safety evaluation of the investigational product(s).

- Promptly notification of all concerned investigator(s)/institution(s) and the regulatory authorities of findings that could
  - Affect adversely the safety of subjects,
  - Impact the conduct of the trial, or
  - Alter the EC/IRB the approval/favourable opinion to continue the trial.
- The Adverse Drug Reaction Reporting
- Expedite the reporting to all concerned investigator/institutions, to the EC/IRB, where required, and to the regulatory authorities of all adverse drug reactions that are both serious and unexpected.
- Complying expedited reports with the applicable regulatory requirement and with the ICH Guideline for the Clinical Safety Data Management: Definitions and Standards for the Expedited Reporting.
- The submission to the regulatory authorities all safety updates and periodic reports, as required by the applicable regulatory requirement.

➢ The Monitoring

➢ The Audit

➢ The Premature Termination or Suspension of a Trial

- The promptly information on the investigators/institutions, and the regulatory authorities of the termination or suspension and the reason for the termination or suspension.
- The promptly information on the EC/IRB for the reason of the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement.

➢ The Clinical Trial/Study Reports

- The submission of the clinical trial reports to the regulatory agencies as required by the applicable regulatory requirement whether the trial is completed or prematurely terminated.

- Ensuring that the clinical trial reports in the marketing applications meet the standards of the ICH Guideline for the Structure and Content of Clinical Study Reports.

http://www.emea.europa.eu/pdfs/human/ich/013595en.pdf

20. Cost of Clinical Trials

For many researchers trying to launch the projects without funding, the cost of the industry-driven research is prohibitive. Depending on the complexity of the study, the number of the study centres, and other factors, the costs can range at least from 5,000 to 20,000 Euro per patient for a randomised trial organised by the industry. Simplifying the organisational procedures could make it possible to reduce these costs. In contrast to the United States, the institutions of the European Union accord a limited portion of the total available funding to the clinical trial. The American National Institutes of Health (NIH) provide a centralised framework with the considerable financial resources, with an annual budget of 28 billion US dollars, of which 31% is allocated to the clinical trial. The NIH is capable of supporting several thousand research projects. In Europe, however, the situation is more fragmented and heterogeneous. There are considerable disparities between the funding allocations and the research potential in the EU member states, creating a climate in which the research is often duplicated, and institutional funding hard to obtain. From one country to another, the research varies greatly both in the quality and in the quantity. The 7th Framework Programme[50] of the EU aims to address these structural problems by creating a more favourable environment for the research, with the better integrated structures through the networks of the excellence and simplified administrative procedures. Within the 7th Framework Programme, the life sciences represent only one branch. The basic science will receive a greater

[50] The 7th Framework Programme for the research and technological development is the EU's instrument for funding the research over the period 2007 to 2013. It bundles all research-related EU initiatives together under a common roof playing a crucial role in reaching the goals of the growth, competitiveness and employment.

proportion of the available resources than the clinical trial, so the concrete impact of this programme on funding for the clinical trial remains to be seen. However, the centralised funding from the EU institutions is not the only possibility for finding the funds for the research in Europe. Many nations reserve a portion of their national budget for funding the research, and these channels have proven their efficacy in the past in several countries. The European Science Foundation (ESF) is an association of the major national funding agencies devoted to the scientific and clinical trial throughout 27 countries. The proposal is to pool the funding from the different organisations and countries to channel it into four to five major projects per year. The ESF takes the responsibility of finding the financial support from its members and affiliate bodies.

20.1. Cost for Patient Enrolment

For people interested in participating in a clinical trial, one of the primary concerns is covering the trial's costs. The clinical trials involves two types of the costs:

- The patient care costs, and
- The research costs.

20.1.1. Patient Care Costs

The patient care costs are usual the care costs that a participant would have even if he or she were not enrolled in a trial e.g.:

- The doctor,
- The hospital,
- The laboratory expenses,
- The diagnostic expenses (e.g. CT, ultrasound),

- The procedure expenses (e.g. surgical procedures),
- The treatment costs, and
- The procedures included in the trial.

20.1.2. Research costs

The costs involved with collecting and analyzing the trial's data for the research purposes are called the research costs. These costs are typically covered by the sponsor of the trial. The sponsors of the clinical trials usually supply the IMP to the participants at no cost.

20.2. Institutional Support for Clinical Trial

The declining interest and incentives in the clinical trial have led to a scarcity of the physician-scientists adequately trained in the research. The inadequate funding for the clinical trial leads to the lower salaries than those available in the private sector, and less attractive career opportunities combine to widen the gap between the clinical and basic research. Promises by the EU nations to increase the proportion of the GNP[51] devoted to the research have yet to be fulfilled. In addition, the strong position of the industry in directing the research has attracted many physician-scientists away from the academic medicine.

[51] Gross National Product (GNP) is the total value of final goods and services produced in a year by a country's nationals.

21. Statistical Consideration

The statistics can be defined as a body of the methods for learning from the experience – usually in the form of the numbers from many separate measurements showing the individual variations. The statistics represents a range of the possibilities experienced by a particular group of the patients. The statistics cannot represent all possibilities that all patients will experience forever no matter what they do. They are not fate written in the stone. The statistical evidence will allow choosing the treatments that seem to give the best results and avoid those which don't work.

The statistical significance is about deciding whether the differences observed between the groups in the experiments are "real" or whether they might well just be due to the chance. The groups can be the patients who were given the different treatments as in a randomized trial. They can also be the groups of the patients with the different characteristics. For example in a clinical trial the patients were randomly assigned to either the Treatment A or Treatment B. Treatment A has a cure rate of 100% and the Treatment B has a cure rate of only 50%. Is the difference real, or is the difference just due to the chance? The bigger the difference between the groups the less likely it is that it's due to the chance. The larger the sample size (number of patients) is the more likely it is that the observed difference is close to the actual difference.

21.1. Observational Study

In a controlled observational cohort study, two groups of the subjects will be selected from two populations that differ in only one characteristic at the start time. The both groups of the subjects will be studied for a specific period and contrasted at the end of the study period. For instance, the smokers and non-

smokers are studied for a period of 10 years, and at the end the proportions of the smokers and non-smokers that died in that period are compared.

21.2. Intervention Study

In an intervention study, the subjects will be selected from one population with a particular characteristic present, then immediately after the baseline, the total study group is split up into a group that receives the intervention and a group that does not receive that intervention. The comparison of the outcomes of the two groups at the end of the study period is an evaluation of the intervention. For instance, the smokers can be divided into those who will be the subject to a smoking-cessation program and those who will not be motivated to stop the smoking. The intervention has the intention to improve the condition of an individual or a group of the individuals.

21.2.1. Controlled Clinical Trials

The controlled clinical trials constitute an important class of the intervention studies. The aim of these trials is to compare the effectiveness and the safety of the two (or more) medical treatments or surgical operations or combinations thereof. The two groups (intervention and control) should be comparable at the start. More specifically, at the baseline, the two groups has to be selected from the same population – only in that case a difference between the two groups at the end of the study is a sign of an effect of the intervention.

21.2.2. Aspect of an Intervention Study

The first step in any intervention study is to specify the target population, which is the population to which the findings should be extrapolated. This requires a specific definition of the subjects in the study prior to the selection.

In a clinical trial, this is achieved by specifying the inclusion and exclusion criteria. In general, the inclusion criteria specify the type of the patients who need the treatment under the examination and the exclusion criteria exclude the patients for which there will be most likely the safety concerns or for which the treatment effect might not be clear, for example, because they are already on the another competing treatment.

21.3. Design of Clinical Trial

The typical clinical trial design varies with the phase of the drug development. For instance, in the Phase-I studies, the analysis of the variance design comparing the different doses are often encountered. In the Phase-II studies, the crossover designs, whereby the patients are randomly assigned to the treatment sequences, are common. In the Phase-III studies, the most common design is the simple parallel-group design where the two or more groups of the patients are studied over time after the drug administration. When two (or more) types of the treatments are combined a factorial design is popular allowing the estimation of the effects of each type of the treatment.

Most of the clinical trials are superiority trials with the aim to show a better performance of the new drug compared to the control drug. When the control drug is not the placebo but a standard active drug, and it is conceived to be difficult to improve upon the efficacy of that standard drug, one might consider showing that the new drug has comparable efficacy. When the new drug is believed to have the comparable efficacy and has other advantages, for example, a much cheaper cost, a non-inferiority trial is an option. For a non-inferiority trial, the aim is to show that the new medication is not (much) worse than the standard treatment.

21.3.1. Parallel Design

The clinical trial of the medical treatments often compare two or more groups of the patients treated separately but concurrently as part of the same study. The parallel comparisons include most of the usual forms of the randomized clinical studies, as well as some nonrandomized studies. If the patients who are assigned to the separate treatment groups differ before the treatment in the factors that affect the prognosis, such as age, extent of the disease, or the concurrent medical problems, the observed results may be affected by this difference as well as by the treatment. The assessment of the treatment effects is then biased[52]. Such factors are called the covariates. There are three common ways to resolve or reduce the problem of the imbalance of the covariates.

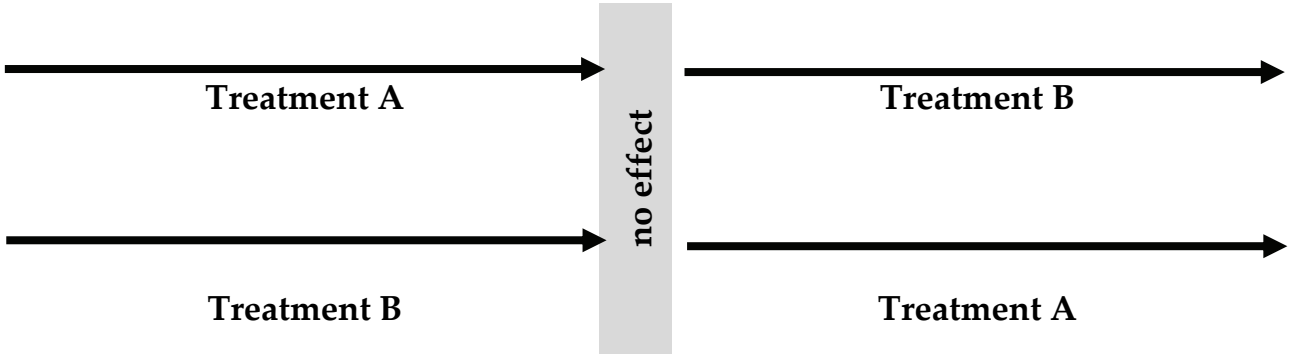
- The randomization is designed to prevent the serious imbalance.
- The stratified analysis can reduce the imbalance problems when they occur.
- The model-based adjustment can reduce the imbalance problems when they occur.

These methods can often be combined. For example, the pairs of the patients could be matched on one or more important background variables (a form of stratification) and then a randomly chosen member of the pair is assigned to an experimental treatment, the other to the control (a form of blocking). In the parallel studies, issues of the bias, comparability, and the sources of the variation other than the treatment revolve around the assessment and control of the effects of the prognostic factors or covariates.

[52] The bias means to have a preference to one particular point of the view or ideological perspective.

21.3.2. Cross-Over Design

In a two-treatment cross-over study, each patient's response under the treatment A is compared with the same patient's response under the treatment B, so that the influence of the patient characteristics that determine the general level of response can be "subtracted out" of the treatment comparison. In the cross-over design, the patients may get the both treatments, the overall survival becomes difficult to analyze as an endpoint. Instead, the typical endpoint for the cross-over trials is the time until the disease becomes measurably worse, known as the time to the progression.



If the variation in the patient characterization accounts for much variation in response, a cross-over design based on a small sample of the patients can provide the same statistical accuracy as a larger parallel study. By choosing between the parallel and cross-over designs five factors that determine the effectiveness of the cross-over design has to be considered:

- The carry-over on the treatment outcomes. The therapeutic effects of the first treatment may persist during the administration of the second. This influence can be minimized by appropriately delaying the second treatment administration.
- The period effects on the treatment outcomes. The disease may progress, regress, or fluctuate in severity during the period of the investigation.

- The treatment sequencing and the patient assignment. The best way to assign each patient to an initial treatment is the randomization. If there are more than two treatments or more than one administration of the treatments, the randomization must specify the sequence.
- The cross-over rules and the timing of the measurements. A previously cross-over rule strengthens the scientific and clinical validity of a study. There are two types of the cross-over rules.
  - Time dependent. Switch in the treatments after a specific length of time.
  - The disease state dependent. A cross-over occurs when indicated by the clinical characteristics of the patient.
- The dropouts, faulty data, and other data problems. The dropout rates can be high in the cross-over studies, since the patients must receive at least two treatments to provide a complete data point. The partial information on a patient completing one treatment and then dropping out can be used in estimating the effects in the Period I, provided that dropout is not related to the treatment response. A high dropout rate greatly weakens the study, and the initial sample size should be sufficiently large to compensate for this effect.
- The statistical analysis. The observations made repeatedly in the same patients tend to be more similar than those made in the different patients. The statistical analysis that take this relation into account are more complicated but more potentially powerful than those that are appropriate for a parallel comparison. The proper statistical analysis begins in effect by comparing the data from a single patient over time and then combines those comparisons across the patients.
- The sample size.

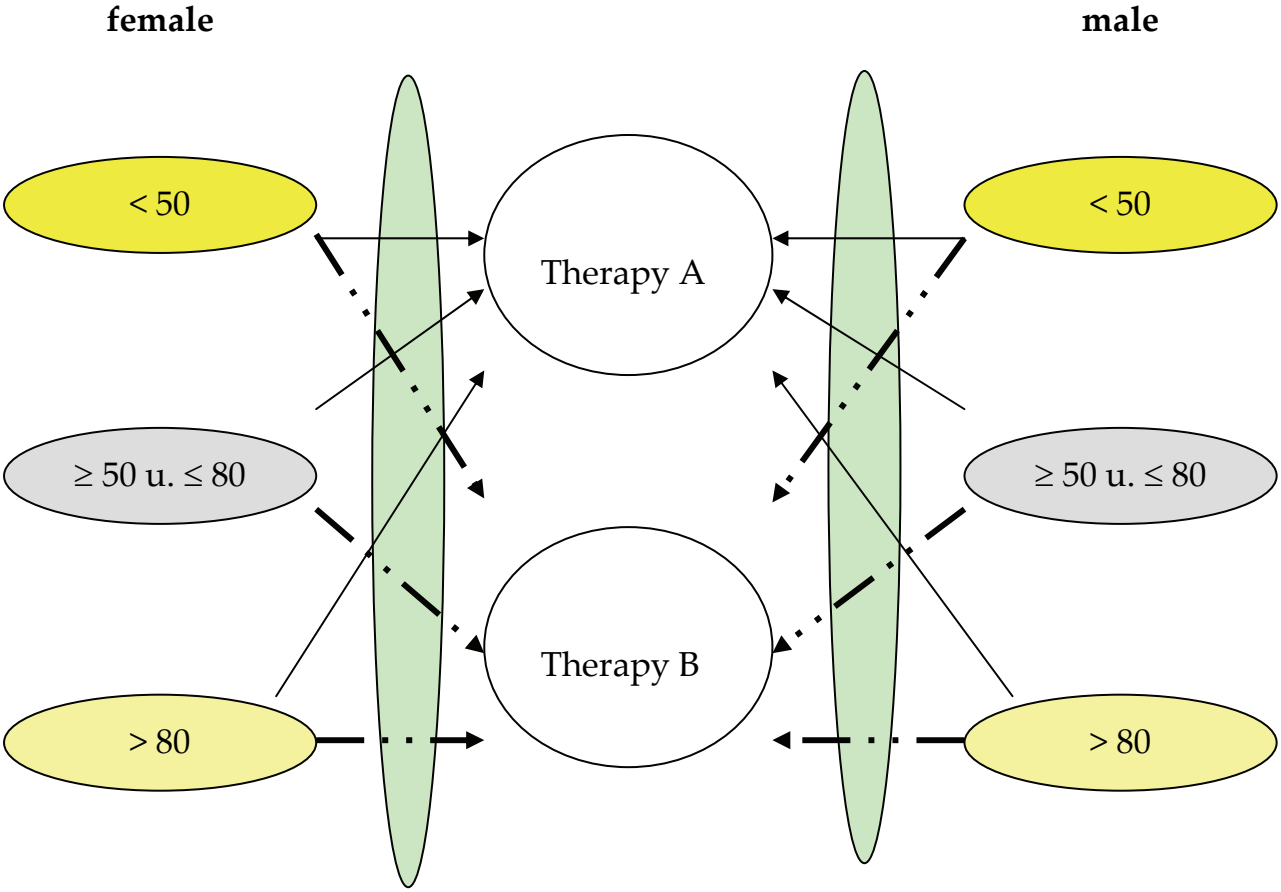
21.3.3. Randomized Trials

The comparability or balance at the baseline is achieved by randomly allocating the subjects to the two groups this is known as the randomization. Simple randomization corresponds to tossing a coin and when (say) heads, the subject will receive the intervention and in the other case the subject will be in the control group. But the other randomization schemes exist, like the block- and stratified randomization. It is important to realize that the randomization can only guarantee the balance for the large studies and that the random imbalance can often occur in the small studies. The randomized trials involve the evaluating not just one, but at least two different treatments, significantly increases the complexity of the decision making.

The randomization, while held to be the best way of getting the reliable answers, becomes ethically controversial if the participants, the patient, believe that the treatments in a trial are in some important sense unequal due to the complexity and controversy. In order to ethically conduct a randomized trial, there has to be a belief that the both treatments are equal, or, more accurately, given that the trial is being conducted because it is not known which treatment is better, it has to be uncertain which treatment is better. If there is sufficient uncertainty about which are the best the trial is considered to be ethical. It has been argued that it is ethical for a doctor to offer a randomized trial to his patient even if he personally thinks one of the treatments is better, as long as it can be said that there is uncertainty in the medical community as a whole. The equality of the treatments is not a simple matter of equality of the estimated efficacy. The treatments vary not only in the efficacy, but also in other very important qualities, such as the nature and

degree of the side effects and risks. Two treatments which truly have the equal evidence of the efficacy may not be at all equal.

Example: In a randomised trial the stratification for the gender (female, male) and weight (< 50 kg; ≥ 50 und ≤ 80 kg; > 80 kg) will result follow:



The purpose of the randomization is to eliminate any potential systematic difference between the patients in the arms of the trial. If the patients or their doctors choose their treatment, there might be some difference in the patients who entered one arm compared to those who selected for the other. If one treatment is more toxic, the patients who are in better shape might tend to choose that arm, and they might tend to do better because they are in better shape. A systematic difference could also mask the differences between the treatments. For these reasons, the randomized trial is almost universally held

to be the gold standard for the reliable conclusions about whether a new treatment produces the real benefits. The advantage of the randomization (plus blinding in a clinical trial) is that the analysis of the results can often be done with the simple statistical techniques such as an unpaired t-Test for the continuous measurements or a chi-squared test for the categorical variables. This is in contrast to the analysis of the controlled observational cohort studies where the regression models are needed to take care of the imbalance at the baseline since the subjects are often self-selected in the two groups.

21.3.4. Stratification

The stratification may also refer to a process to control for the differences in the confounding variables, by making the separate estimates for the groups of the individuals who have the same values for the confounding variable.

21.3.5. Placebo Controlled Trials

Most interventions aim to achieve a change in the attitude (a psychological effect) the medical treatments need to show their effectiveness apart from their psychological impact, which is also called the placebo effect. The placebo effect is the pure psychological effect that a medical treatment can have on a patient. This effect can be measured by administering the placebo (inactive medication with the same taste, texture, etc. as the active medication) to the patients who are blinded for the fact that they haven't received the active treatment. The placebo controlled trials are the trials with a placebo group as the control group. When only the patient is unaware of the administered treatment, the study is called the single-blinded. Sometimes, also the treating physician needs to be blinded, if possible, in order to avoid the bias in scoring the effect and safety of the medication. When the patients as well as physician are

blinded, we call it a double-blinded clinical trial. Such a trial allows distinguishing the biological effect of a drug from its psychological effect.

21.3.6. Blinding

Blinding is used for the eliminating risk of the expectation influencing the findings. In the controlled trials the term blinding, and in particular "double blind" usually refers to keeping the study participants, those involved with their management, and those collecting and analysing the clinical data unaware of the assigned treatment, so that they can not be influenced by that knowledge.

The relevance of blinding will vary according to the circumstances. Blinding the patients to the treatment they have received in a controlled trial is particularly important when the response criteria are the subjective, such as the alleviation of the pain, but less important for the objective criteria, such as death. Similarly the medical staff caring for the patients in a randomised trial should be blinded to the treatment allocation to minimise the possible bias in the patient management and in assessing the disease status. For example, the decision to withdraw a patient from a study or to adjust the dose of the medication could easily be influenced by the knowledge of which treatment group the patient has been assigned to. In a double blind trial neither the patient nor the physician are aware of the treatment assignment.

21.4. Size of Sample

By designing a clinical trial to detect a possible difference between the treatments, there is the need to have a large enough sample size so that if there is a difference big enough. The smaller the real difference between the treatments is, the more patients are needed to be likely to detect a statistically

significant difference in a clinical trial. The larger the real difference is, the fewer patients are needed to detect a statistically significant difference in an actual clinical trial. For the scientific and ethical reasons the sample size for a trial needs to be planned carefully with a balance between the clinical and statistical considerations. Ideally, a study has to be large enough to have a high probability (power) of detecting, as statistically significant, a clinically important difference of a given size if such a difference exists. The size of the effect deemed important is inversely related to the sample size necessary to detect it, that is, large samples are necessary to detect the small differences. The elements of the sample size calculation are:

- The estimated outcomes in each group (which implies the clinically important target difference between the intervention groups),
- The alpha (Type I) error level,
- The statistical power (or the beta Type II error level), and
- For the continuous outcomes, the standard deviation of the measurements.

21.5. Statistical Tests

The statistically significant means that it is unlikely the treatments have the same success rate, but it's quite likely that the real difference between the treatments is not exactly the observed difference. So if the Treatment A has a 57% success rate and the Treatment B a 46% success rate and the difference is statistically significant, this does not mean these are the exact true success rates. It only means that it's unlikely that the advantage of the Treatment A is entirely due to the chance. It may be that there is a difference, but not enough people were included in the test for the difference to show as statistically significant. If a trial is too small, it's even possible that there's a big and meaningful difference between the treatments but hardly any difference was

actually seen - just due to the chance. When there is a negative result the "power" of the trial has to be considered for detecting the meaningful differences as statistically significant.

The use of the different statistical tests is depending on what kind of the data is being tested and what statistic is being tested - say the mean or the median. Each of these tests is a mathematical procedure which has a unique set of the assumptions.

- The Fisher's exact test
- The Student's t test
- The Chi-Squared test
- The Mann-Whitney test
- The Log Rank Test
- The Pitfalls

21.5.1. P-Value

The statistical testing, "p-Values", and statistical significance works by assuming that the groups are actually the same - that there is no difference - and then mathematically estimating the probability that a difference between the groups is at least as big as the one - just due to the chance. This probability is called 'p' and is referred to a "p-value". The p-values range from 0 to 1 where 0 means no chance and one means certainty. 0.5 means a 50% chance and 0.05 means a 5% chance. If the p-value is relatively large, so that the chances are relatively high that the difference could have arisen by the chance alone then the results are at least consistent with the idea that there is no real difference between the groups for the characteristic being tested. But p-value is very small the results are not consistent with the idea that there was no real difference between the groups, or at least it is very unlikely that there is no

difference. By the convention if the $p<0.05$ the difference is said to be "statistically significant. The $p<0.05$ means that the probability is less than 5 percent that the observed difference was due to the chance alone.

21.5.2. Power of Experiment

Given the minimum difference we want to detect, and the p-value we require to declare the results statistically significant (usually 0.05) for any sample size, we can calculate the probability to detect a statistically significant difference. The probability is the power of the experiment. A trial which doesn't have enough patients is often called "underpowered". The underpowered trials risk can not find the real differences even when they are there.

21.5.3. The Null Hypothesis

The "Null Hypothesis" is the hypothesis that the treatments being compared are all the same. Only if enough evidence accumulates - in the form of a statistically significant difference from an experiment - is the null hypothesis "rejected". So "rejecting the null hypothesis" just means finding a statistically significant difference.

21.5.4. Type I and II Errors

A Type I Error will occur when the result is a false positive - deciding that there is a real difference when in fact there is no difference. If the $p=0.05$ then there is a 5% chance of a type I error. Type I error is also called the "alpha error".

A Type II Error will occur when the result is a false negative - that is there is a real difference but the statistical test fails to show the difference to be

statistically significant. The chance of a type II error is estimated with the power of the experiment. The Type II error is also called the "beta error".

21.5.5. Explanatory Models

The explanatory models are often used to identify the risk factors that are associated with the outcome of the interest in an exploratory study. In other cases, the primary focus is on the relationship of the outcome with a specific risk factor but there is concern that either the relationship between the risk factor and outcome may be confounded by other factors or strength of the relationship may be modified by an interaction term. The clinical experience and expertise can be of the considerable importance in the modelling process in identifying the potential confounding factors and effect modifiers in advance of the study.

Confounding: The confounding occurs when the apparent association between a risk factor and the outcome is altered by the relationship of each to a third factor. Such confounding may obscure a real relationship or created an apparent relationship when one does not actual exist. The multivariate methods permit the study of the risk factor-outcome relationship adjusted for the other known and measured cofactors, which may confound the relationship. Although the confounding can also be addressed to some extent through a stratified analysis, the multivariate models have the advantage of dealing with the multiple confounders simultaneously potentially incorporating all of the subjects. It must be noted that such analyses can only adjust for the potential confounding factors that are actually considered, measured and included in the analysis. The confounding may still exist with the factors that are unknown, unmeasured or otherwise left out of the model. When the focus is on the identification or evaluation of the specific risk factors,

the model permits the study of the independent contribution of each to the outcome. When the analysis is focused on one main variable, its relationship with the outcome can be estimated and adjusted for all of the potential confounding factors included in the model.

Interaction: Dealing with the potential interaction can be one of the most challenging aspects of developing the risk models. Interaction or effect modification represents the situation where the interacting variable alters the level of the association between a risk factor and outcome. It is very important that the potential interaction terms be considered *a priori* as the evaluation for the interaction involves the subgroup analyses and multiple testing issues. While an interaction factor may also be a confounding term, the confounding and interaction must be dealt with differently. The confounding can often be adequately dealt with by including such a factor in the risk model and adjusting for its effect. Interaction can be assessed either in the stratified analysis or by incorporating an interaction term as the product of the effect modifier and the risk factor into the model. If there is no significant interaction, the interaction term can essentially be ignored. In situations where there is significant interaction, such as with the gender, a single model without an interaction term will provide an 'average' effect that may not be correct for either men or women. To properly deal with the interaction, the investigator can present the model with the interaction term as well as the effect modifier and risk factor in the model. Such models are often complex and difficult to explain since the relative risk estimates such as the odds ratios or hazard ratios are no longer simply numbers based on a single coefficient but rather an equation where the relative risk is a function of the interaction term and will change as the value of the interaction term changes. Alternatively, the investigator may choose to present the separate models for the different levels

of the interaction term, e.g., different models for males and females. The outcome differences between the subgroups should be assessed by testing the interaction between the risk factor and the interaction variable rather than by the separate analyses within the subgroups, which may have limited power due to the small sample size.

Risk Factors: The selection of the risk factors for the inclusion in a model represents perhaps the most challenging issue with regard to the risk modelling. Ideally, such models should include all relevant and important risk factors and their potential confounders. Often risk factors are identified through the use of a statistical model using exploratory techniques such as the forward or backward stepwise variable selection methods. Since such an approach selects variables to fit the specific set of the data, it is fraught with many potential problems including the model instability and exaggeration of the relative risk estimates and their associated level of significance. A more valid approach is the selection of the risk factors based on a fundamental understanding of the pathophysiology of the disease and pharmacology of the treatment, the prior knowledge and experience as well as those found to be significant in the univariate analysis.

Statistical Models: The specific model or mathematical relationship between the risk factors and outcome chosen depends upon the type of the outcome being studied and anticipation that the data will approximately follow the relationship of the model. In the multivariate analyses, a coefficient or 'slope' is estimated for each independent variable by fitting a certain model to the data while adjusting for all of the other variables. Commonly used models include:

- The linear regression modelling of the mean of the normally distributed continuous outcome measures such as the heart rate as a linear function of the independent variables,
- The logistic regression modelling the probability of a dichotomous (yes/no) outcome as the multiplicative product of the individual predictors, and
- The cox proportional hazards regression modelling the risk of a discrete event over the time (survival) as the product of the individual predictors.

21.5.6. Descriptive Analysis

Each study measure should be assessed individually for:

- Completeness for the missing data. The missing data may include both missing or late measures as well as the patients lost to follow-up or removed from the study prematurely. The missing data must also be evaluated for any relationship with the primary outcomes or any of the prognostic/predictive variables. If any variable to be used in further analysis has more than 5% missing data, consideration should be given to using one of the available imputation techniques.
- Consistency.
- Quality.

Modeling: the univariate and multivariate models may be generated to define the risk of the individual events as well as the composite outcomes likely to have a combined impact on the risk. The covariates likely to affect the probability of the primary outcomes including the risk of the mortality, complications as well as the resource utilization or direct medical costs will be evaluated alone and in combination. The models should include as covariates each treatment agents and their possible interaction as well as factors of the

known prognostic significance. These models will generally be of the fixed size incorporating either:

- The pre-treatment information (demographic factors, medical history and clinical factors), or
- The limited number of the fixed models incorporating both the pre-treatment information and the results of the first treatment cycle.

21.5.7. The Median

The statistics recognizes different measures of an "average," or central tendency. The median, a different measure of the central tendency, is the half-way point. For example line up five kids by the height, the median child is shorter than two and taller than the other two. A politician in power might say with pride, "The mean income of our citizens is 15,000 € per year." The leader of the opposition might retort, "But half our citizens make less than 10,000 € per year." The first invokes a mean[53], the second a median.

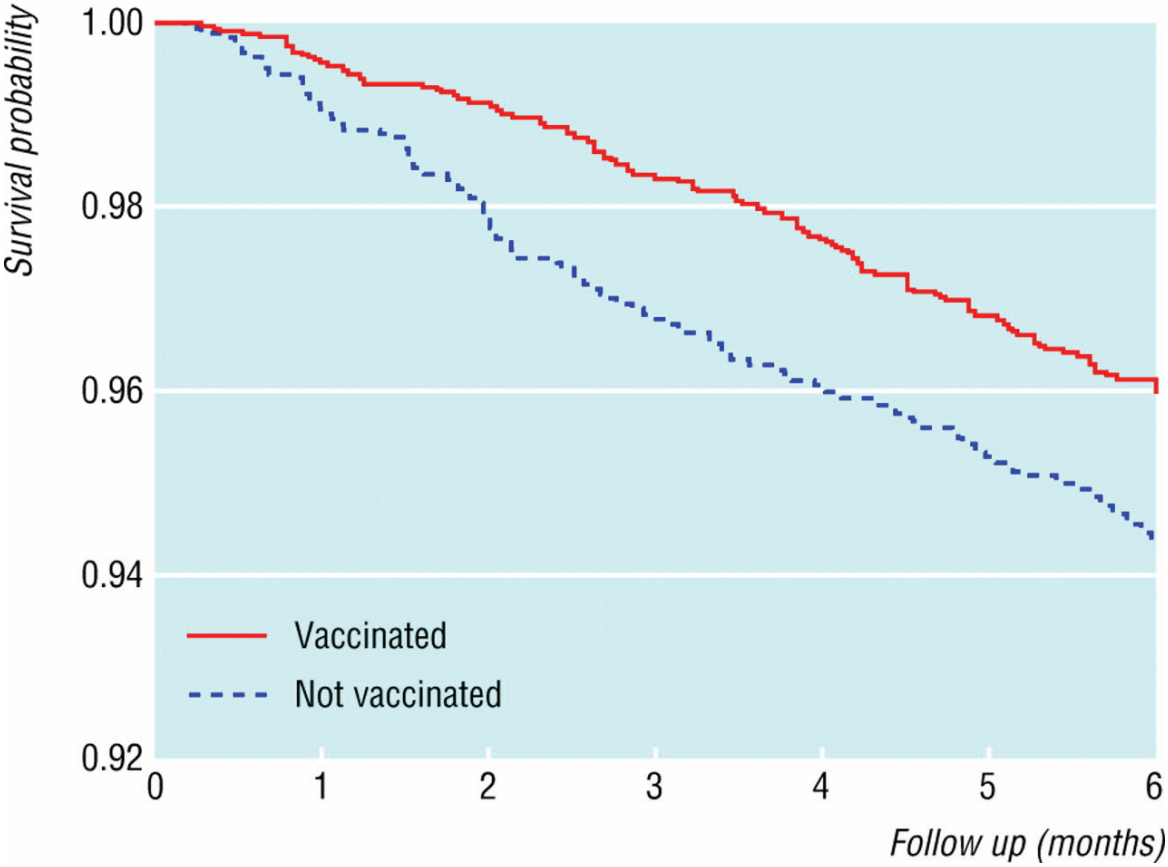
21.5.8. Survival Curves

The survival curves usually are about the patients who were all treated a certain way. The survival curves, interpreted correctly, chart the way the odds change over the time. Most real life survival curves usually shown as the staircase curves with a "step" down each time there is a death. This is because a real-world survival curve represents the actual experience of a particular group of the people. At the moment of each death, the proportion of the survivors decrease and the proportion of the survivors do not change at any

[53] The mean is our usual concept of an overall average - add up the items and divide them by the number of shares. Means are higher than medians in such cases because one millionaire may outweigh hundreds of poor people in setting a mean, but he can balance only one mendicant in calculating a median.

other time. Thus the curve steps down at each death and is flat in between the death which leads to the classic staircase appearance.

Five year survival or the median survival is just a single point on the survival curve - just one dot from the whole picture. The basic meaning of five year survival is self explanatory. The median survival is the time at which the percentage surviving is 50%. If more than half the patients are cured, there is no such point on the survival curve and the median is undefined.



Kaplan-Meier survival curves for children who did and did not receive the BCG vaccine. The six months follow up of 5274 children aged 0-6 months at the initial visit, Guinea-Bissau, 1990-1996[54]

[54] Ines Kristensen, Peter Aaby, Henrik Jensen. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. BMJ 2000;321:1435

21.6. Interim Analyses from Randomized Trials

The design of the randomized trials often includes the analyzing the data at predefined time during the trial. If the data sufficiently favours one arm, no further patients will be accrued. This both protects the patients from being treated with the known less effective or more toxic treatment, and potentially shortens the trial. In the most rigorous form of the interim analysis, an Independent Data Monitoring Committee analysis the data at the pre-determined times and decides whether the trial should be stopped. The detailed information on how each arm is faring is kept from the investigators who treat the patients. It also turns out that for the subtle statistical reasons, the data has to favour one arm particularly strongly before the trial is halted. So the mere fact that the trial has passed an interim analysis tells us very little about whether one arm is doing significantly better.

21.7. Endpoint in Clinical Trial

An endpoint is something which is measured in a clinical trial or study. Measuring the selected endpoints is the goal of a trial. The response rate and survival are examples of the endpoints.

21.7.1. Disease Free Survival

The Disease Free Survival is usually used to analyse the results of the treatment for the localized disease which renders the patient apparently disease free, such as surgery or surgery plus adjuvant therapy. In the disease free survival, the event is relapse rather than death. The people who relapse are still surviving but they are no longer disease-free. Just as in the survival curves not all patients die, in Disease Free Survival curves not all patients relapse and the curve may have a final plateau representing the patients who

didn't relapse after the study's maximum follow-up. Because the patients survive for at least some time after the relapse, the curve for the actual survival would look better than Disease Free Survival curve.

21.7.2. Progression Free Survival

The Progression Free Survival is usually used in analysing the results of the treatment for the advanced disease. The event for the progression free survival is that the disease gets worse or progresses.

21.7.3. Response Duration

The response duration is occasionally used to analyze the results of the treatment for the advanced disease. The event is progression of the disease (relapse). This endpoint involves selecting a subgroup of the patients. It measures the length of the response in those patients who responded. The patients who don't respond aren't included.

21.8. Censoring Data

Mathematically removing a patient from the curve at the end of their follow-up time is called "censoring" the patient. Censoring a patient will reduce the sample size of the patients at the risk after the time of the censorship. Reducing the sample size always reduces reliability, so the more patients are censored and the earlier they are censored the more unreliable the results are. Many clinical trials are designed with a minimum follow-up time. This means that the results aren't reported until that amount of the time after the last patient signed up for the trial. Often reports of the preliminary results don't include any minimum follow-up time and include the patients with very short follow-up time which definitely affects the reliability of the result.

21.9. Analysis of Clinical Trial

Failure to include all participants in the analysis may bias the trial results. Most trials do not yield perfect data, however. "Protocol violations" may occur, such as when the patients do not receive the full intervention or the correct intervention or a few ineligible patients are randomly allocated in error. Despite the fact that the most clinical trials are carefully planned, many problems can occur during the conduct of the study. Some examples are as follows:

- The patients who do not satisfy the inclusion and/or exclusion criteria are included in the trial,
- A patient is randomized to the Treatment A but has been treated with the Treatment B,
- Some patients drop out from the study, or
- Some patients are not compliant, that is, do not take their medication as instructed, and so on.

21.9.1. As-Treated

The as-Treated analysis has the general idea to compare the subjects with their treatment regimen that they received. It does not consider the fact which treatment they were assigned for the treatment.

21.9.2. Intention-to-Treat

The randomized clinical trials analyzed by the intention-to-treat (ITT) approach provide the unbiased comparisons among the treatment groups. Since it came up in the 1960s, the principle of the ITT has become widely accepted for the analysis of the controlled clinical trials. In the ITT population, none of the patients is excluded and the patients are analyzed according to the

randomization scheme. Although the medical investigators have often difficulties in accepting the ITT analysis, it is the pivotal analysis for the FDA and EMEA. The ITT analysis is generally favoured because it avoids the bias associated with the non-random loss of the participants. The ITT analysis is not appropriate for examining the adverse effects. Although the statistical techniques employed in the clinical trials are often quite simple, recent statistical research tackled specific and difficult the clinical trial issue, like the dropouts, compliance, non-inferiority studies, and so on. Probably the most important problem is the occurrence of the dropout in a clinical trial. For instance, when the patients drop out before a response can be obtained they cannot be included in the analysis, even not in an ITT analysis.

The basic ITT principle is that participants in the trials should be analysed in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention. Two issues are involved here. The first issue is that the participants who strayed from the protocol (for example by not adhering to the prescribed intervention, or by being withdrawn from active treatment) should still be kept in the analysis. An extreme variation of this is the participants who receive the treatment from the group they were not allocated to, who should be kept in their original group for the analysis. This issue causes no problems provided that, as a systematic reviewer, you can extract the appropriate data from the trial reports.

- The rationale for this approach is that, in the first instance, we want to estimate the effects of allocating an intervention in practice, not the effects in the subgroup of the participants who adhere to it.
- The second issue in the ITT analyses is the problem of loss to follow-up. The people are lost from the clinical trials for many reasons. They may die, or

move away; they may withdraw themselves or be withdrawn by their clinician, perhaps due to the adverse effects of the intervention being studied.

If the participants are lost to follow-up then the outcome may not be measured on them. But the strict ITT principle suggests that they should still be included in the analysis. There is an obvious problem - we often do not have the data that we need for these participants. In order to include such participants in an analysis, we must either find out whether the outcome data are available for them by contacting the trial lists, or we must impute (i.e. make up) their outcomes. This involves making assumptions about the outcomes in the 'lost' participants.

21.9.3. Per-Protocol

The analysis can only be restricted to the participants who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment. This analysis is known as an "on-treatment" or "per protocol" analysis. Also, the per-protocol restricts the comparison of the treatments to the ideal patients, that is, those who adhered perfectly to the clinical trial instructions as stipulated in the protocol. This population is classically called the per-protocol population and the analysis is called the per-protocol-analysis. A per-protocol analysis envisages determining the biological effect of the new drug. However, by restricting the analysis to a selected patient population, it does not show the practical value of the new drug.

21.9.4. Last-Observation-Carried-Forward

The most important problem during the performance of the clinical trial is the occurrence of the dropout. For instance, when the patients drop out before a response can be obtained they cannot be included in the analysis, even not in

an ITT analysis. When the patients are examined on a regular basis, a series of the measurements is obtained. In that case, the measurements obtained before the patient dropped out can be used to establish the unknown measurement at the end of the study. The Last-Observation-Carried-Forward (LOCF) method allows to analysis the data. But, the recent research shows that this method gives a biased estimate of the treatment effect and underestimates the variability of the estimated result. Let's assume that there are 8 weekly assessments after the baseline observation. If a patient drops out of the study after the third week, then this value is "carried forward" and assumed to be his or her score for the 5 missing data points. The assumption is that the patients improve gradually from the start of the study until the end, so that carrying forward an intermediate value is a conservative estimate of how well the person would have done had he or she remained in the study. The advantages to this approach are that

- It minimises the number of the subjects who are eliminated from the analysis, and
- It allows the analysis to examine the trends over time, rather than focusing simply on the endpoint.