Association for Good Clinical Practice
And Clinical Research Development in Bulgaria

INSIDE CLINICAL TRIALS

(English Version of the Patient's Brochure "CLINICAL TRIALS – WHAT SHOULD WE KNOW ABOUT THEM" published in Bulgaria, Romania, Serbia and Macedonia)

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Chapter 1

Developing New Drugs

The pharmaceutical industry constantly develops and introduces to medical practice a number of new drugs and formulations. Each one of them undergoes series of tests to prove its effectiveness and safety. Only 5 out of approximately 50 000 newly synthesized drugs reach the clinical phase and are tested on human subjects, and only one of them proves to be effective to receive regulatory approval for manufacturing and marketing.

The drug development process involves the close collaboration of the pharmaceutical industry, leading clinical laboratories and hospitals, regulatory authorities, health authorities, and other institutions. There are two phases in this process – *pre-clinical* and *clinical* one.

The *pre-clinica*l phase involves investigation of the physico-chemical, toxicological and pharmacological effects of the potential drug on live organisms, as well as examination of the possible damages to the cell genetic apparatus. This phase of the medication development process is performed in pharmaceutical and pharmacological laboratories and takes up about 4 years.

The *clinical* phase of the drug development process includes applying the potential drug on humans, while investigating the possible adverse effects on human organs and systems. This phase involves 4 sub-phases (phase I, II, III and IV) performed consecutively. The clinical phase is developed for about 6 years.

During phase I the potential new drug is applied to a small number of healthy volunteers and its effects (which may vary depending on the dose and the dosage form) are assessed. Drug tolerance is determined during this phase: how the drug is absorbed in the human organism, how its chemical composition is changed and how it is excreted.

During phase II the drug is tested on patients to prove its effectiveness. It is performed with patients (between 10 and 200) who are very carefully monitored in clinical centres under the guidance of leading specialists. Data collected during this phase of clinical research is used to determine the appropriate therapeutic dosage of the studied drug as well as its optimal intake.

Phase III is conducted under conditions as close as possible to the ones in which the medication will be prescribed to and used by patients. More than 1000 patients participate in this phase in hospitals and clinics in different countries. It is important to note that the main purpose here is to evaluate the advantages of the new drug to already existing drugs for

treatment of related diseases and conditions, as well as to estimate the number and frequency of adverse reactions. Usually the new drug should successfully undergo several "phase III studies" so that its characteristics be unequivocally confirmed.

Phase IV starts when the studied drug is approved for manufacturing and available on the market (i.e. in pharmacies). This phase actually represents the continuous monitoring of adverse events and adverse reactions (that, although rare, may nevertheless appear) when the drug is prescribed to the general population of patients. New data with respect to recommended dosage and intake may also be investigated.

The discussed phases of clinical trials are only one way to describe the process of developing a new medication. It is important to understand that "phase" is a description of the purposes of a particular stage in a clinical trial and often one type of research may comprise of elements of several phases. However, the accumulated data should determine the efficacy and safety of the studied medication.

Clinical trials do not always reveal new and better treatments. Some trials show that a studied drug does not have the expected effects or that the adverse reactions are more frequent and/or more dangerous than those of the existing standard treatments. However, both positive and negative findings contribute significantly to the development of new methods of treatment and medical research.

Chapter 2

Good Clinical Practice (GCP) Regulations

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve human participants. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trail data are credible.

The main principles of GCP (according to the guidelines of Good Clinical Practice, Chapter 2) are summarized here:

2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki from 1964 (Annex 1) and that are consistent with GCP and the applicable regulatory requirements.

2.2. Before a trial is initiated, the foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3. The rights, safety and wellbeing of the trial subjects are the most important considerations and should prevail over the interests of science and society.

2.4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5. Clinical trials should be scientifically sound and described in a clear, detailed protocol.

2.6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion.

2.7. The medical care given to, and medicinal decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8. Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s).

2.9. Freely-given informed consent should be obtained from every subject prior to clinical trial participation.

2.10. Clinical trial information should be recorded, handled and stored in a way that allows its reporting, interpretation, and verification.

2.11. The confidentiality of records that could identify subjects should be protected, thus respecting the privacy rules in accordance with the applicable regulatory requirement(s).

2.12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.

2.13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

The application of GCP standards inevitably leads to a certain increase of expenditures for conducting clinical trials. However, data collected in these trials is more reliable and the rights of the study participants are protected to a greater extent.

Chapter 3

Conducting Clinical Trials

We are all aware that harmless and cure-all medications do not exist. There are poorly investigated drugs as well as ones that have not been prescribed appropriately. Therefore, controlled clinical trials have been conducted since the beginning of the 1980s to investigate and to develop drugs for fighting diseases.

Clinical research trials are conducted in hospitals, clinics, doctors' offices and research facilities, known as investigational (trial) sites, and are controlled by research consultants.

It is important to understand that each research study is a complex process of interaction between the participating parties and there is constant control over them. The responsibility for conducting the study is shared by the sponsor, the investigator and the monitor, all of whom are overseen by the Competent Regulatory Authorities.

There are rules that guarantee the health and well-being of clinical trial participants and they are called the Good Clinical Practice (GCP) Regulations. Compliance with GCP standards ensures that study participant's rights are upheld, as well as that the results from the trial are objective.

The quality of the study drugs is guaranteed as well by complying with the standards of Good Manufacturing Practice (GMP).

The Sponsor

The sponsor is a pharmaceutical company or a research organization that has succeeded in the development of a new drug for a certain disease and is willing to prove its effectiveness in people.

The role of the sponsor is to design and organize the conducting of the clinical trial. In order to do that it is necessary to equip a team of scientists, physicians, investigators and monitors that work together to develop the plan (protocol) of the study and to execute all the different steps and stages of the clinical investigation. However, the overall supervision of the whole study and the responsibility for its outcome lies with the sponsor.

The Investigator

The Investigator is a doctor who is responsible for organizing and conducting the clinical trial, for taking care of the participants (both patients and healthy volunteers).
It is highly recommended that the investigator is a qualified physician, who has a lot of experience and profound knowledge in the specific area under investigation.

The principal investigator of a trail site should meet the following requirements:

- University degree in Human Medicine (or Dental Medicine, where applicable), as well as license for practicing medicine in the country where the clinical trial will be conducted;
- Certain experience (at least two years) in the medical area, related to the trial;
- Knowledge of the rules and requirements for conducting a clinical trial, as well as GCP training;
- Personal qualities, such as high integrity and professionalism;
- Knowledge of the procedures for identifying and treatment of adverse events and drug reactions.

In addition to his/her participation in the scientific and clinical part of the trial, the principal investigator also has administrative duties. They result from the existing inter-institutional relations, the GCP and the applicable regulatory requirements, and include:

- Work review and ensuring the appropriate qualification of the assistants who take part in the clinical trial;
- Preparation and timely submission of all the necessary reports related to the progress of the trial;
- Keeping any confidential information that is a property of the sponsor from being disclosed;
- Abiding by existing law regulations;
- Management of possible conflicts of interests.

The principal investigator should provide relevant documents in support of his qualification – medical license, resume, GCP training certificates, reports on successfully conducted and finished previous clinical trials, certificates from audits or inspections, others.

Usually the principal investigator assigns at least one assistant, called the co-investigator. The co-investigator should also provide his resume in support of his professional qualifications and experience. The number of the co-investigators depends both on the resources of the research center and on the requirements of the clinical trial. The responsibilities of the co-investigator are assigned by the principal investigator and should be

clearly agreed and documented. They may include: recruitment of patients, assessment of their condition, daily care, paperwork.

Depending on the workload of the clinical center, there might be a clinical trial coordinator assigned – a physician, a nurse or a hospital attendant. The coordinator is not directly involved in recruiting patients or taking care of them. His/her duties are to maintain files related to the clinical trial and to guarantee the keeping of neat records. He/she should always be informed about the number of the participants, the progress of the clinical trial and the forthcoming administrative tasks.

The Monitor

In contrast to the prominent roles of the investigator and the sponsor, the role of the monitor stays in shadow for the participants in the clinical trial. This is because of the specific activities of the monitor and the fact that his/her major duties are to contact the trial site, to control its work and to communicate between the sponsor and the investigators.

It is important for the participants in clinical research that their health and safety are being cared for and observed by other specialists, who oversee the investigators' actions and are there to prevent any possible mistakes and discrepancy in the run of the clinical trial.

Plan (protocol) of a Clinical Trial

The plan (also called protocol) of the clinical trial is a unique document describing in details how the study should be conducted. The sponsor of the study appoints a team of specialists to prepare the protocol - physicians, scientists, statisticians, IT specialists, consultants responsible for the quality of data, etc.

The GCP requirements should be followed when preparing the protocol. Generally it should contain the following:

- Scientific integrity of the trial (trial's objectives);
- Number of research sites where the trial would take place;
- Study methods and details of the procedures that will take place during the trial;
- Description of the statistical and analytical methods that will be used, as well as grounds for the selected number of study participants;
- If a data monitoring committee is involved, there should be details about it (e.g. members, criteria for discontinuation of the trial, frequency of meetings);
- Safety measures for protection of trial data.

Regarding the participants in the clinical trial (both healthy volunteers and patients) the protocol should contain:

- inclusion criteria;
- exclusion criteria;
- reasons for participation of representatives of a vulnerable social group (especially for representatives of groups with limited autonomy and subordinate position);
- intention to involve both men and women in the trial;
- age of participants;
- ethnic and racial distribution of the particular population;
- any potential risks relevant to the trial participation;
- any possible benefits;
- any possible alternative treatment (especially in therapeutic trials) in case the patient refuses to participate;
- methods of recruiting participants;
- details of the informed consent process and of the person in charge of obtaining it;
- description of any additional procedures for people who are not able to give their informed consent according to the standard procedure;
- information about any possible additional expenses as a result of the participation in the trial and their reimbursement.

It is a fundamental duty of each member of the research team conducting a clinical trial to follow the protocol strictly in detail and this is declared in writing by the principal investigator.

Inclusion/exclusion Criteria

The selection of inclusion criteria for recruiting study participants requires deep knowledge of the disease, the study drug, as well as previous experience in planning and conducting clinical trials. These criteria reflect participants' safety and attempt to reduce the potentially wrong or misleading data collected during the trial.

The purpose of the exclusion criteria is to ensure the formation of a homogeneous group of participants for the trial. That is particularly significant for Phase II trials because of the small number of participants and the resulting reduced possibility of using standard statistical methods to prove the effectiveness of the study drug. When exclusion criteria are

not well determined the data collected from the study might be misleading and difficult to interpret.

In most studies the inclusion/exclusion criteria require the following information to be collected:

- Age: The age of the study participants is limited by the scientific or medical requirements of the trial (i.e., stage of development of the study drug, its indications, the objectives of the study, etc.). For example, for phase I trials healthy volunteers aged 18 to 45 are chosen generally. Both children and older patients are excluded from phase II trials as a rule. However, if the study drug is one for treatment of a disease related to age (e.g. Alzheimer's disease), elderly patients will be the target population for this particular phase II trial.
- Sex: It is important that equal number of men and women be enrolled except for studies of drugs targeting only one gender. During the 80's there was a gender disproportion between study participants, when women with childbearing potential were not included in clinical trials because of potential risk for the embryos in case of pregnancy. As a result of this restriction, a few years later pharmaceutical companies realized that there was lack of information about the indications of the study drugs administered to women of this age group. Today there are rules for conducting clinical trials allowing women of childbearing potential to be involved in all phases of if they use appropriate means of contraception. However, it is absolutely not acceptable for both pregnant women and breast-feeding mothers to participate in clinical studies.
- Ethnic background: No ethnic group should be an object of clinical trials if there is a potential risk for the participants, as well as no ethnic group should be excluded from a trial that might be beneficial to them.
- Medical diagnosis: The diagnosis should be defined precisely as it would not be ethical to involve a patient with an unknown disease. However, this is not applicable for most Phase I trials as they are conducted with healthy volunteers.
- Stage and severity of disease: This criterion depends on the objectives of the trial. Generally, patients experiencing severe attacks of a disease should not be involved in a trial, especially in the initial stages of development of study drug.

Chapter 4

Involving Patients in Clinical Trials

In 1979 the US National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research publishes the Belmont report. It states the basic ethical principles for research involving human subjects: respect for human beings, beneficence, and justice. Furthermore the report gives rise to moral requirements for procedures in the selection of research subjects.

The principle of justice requires impartial distribution of the benefits and burdens of research among the participants. It is reviewed at two levels: social and individual justice.

Social justice requires that distinction is drawn between populations that might, and might not, participate in research. Thus, it can be considered a matter of social justice when in a clinical trial, certain groups should bear burdens of the study before others – e.g. healthy volunteers are chosen before patients, and adults before children. Social justice may be achieved by well-defined recruitment (i.e. inclusion and exclusion) criteria.

Individual justice requires that investigators treat fairly all clinical trial participants. They should not offer participation in potentially beneficial trials to patients whom they favour. The exclusion of groups or individuals from participation in clinical trials should always be preceded by a very careful and detailed assessment.

Recruiting participants (both patients and healthy volunteers) is one of the most significant and crucial points in conducting a clinical trial. It is mandatory to abide by the fundamental regulations that guarantee the safety of the participants and the authenticity of the data.

Patients' information during the clinical trial

Informed Consent Form *(or what is expected of you if you would like to take part in a clinical trial and what can you expect from your participation in that trial)*

This is the form that has the greatest significance for you as a participant in any clinical trial. It comprises of a detailed description of the study participation procedures, the rights and obligations of each party, the insurance against any possible injury during the participation, as well as additional information about the participants (compensations for travel expenses, emergency contacts, what should be done in case of infringement of

patient's rights). The informed consent should be signed and dated both by the investigator and the participant in the clinical trial. The original form is usually kept in the investigator's file and the participant is provided with a copy of the form.

The Informed Consent Form usually consists of two combined documents:

1. Patient Information (brochure);
2. Signature page.

The plan of the clinical trial (what will happen during the trial), as well as all the details of the study, including the expected benefits and risks for the participant's health, are thoroughly described in the first part.

It is necessary that you be given the opportunity to get acquainted in details with the Informed Consent, as this is a large document (sometimes the form consists of more than 10 pages) that is difficult to be read and absorbed at once. It is your right to be given the opportunity to read it carefully in detail, and to receive satisfactory answers to your questions.

By signing this form you guarantee that you will abide by the protocol of the clinical trial and follow the instructions of your doctor. The investigators also guarantee abiding by the protocol thus minimizing the potential risk for your health.

The Informed Consent Form is not an impromptu text given to you by your investigator to sign. This fundamental document is structured in accordance with the principles of GCP. A long and complex procedure (comprising of 18 to 21 compulsory elements) should be followed when preparing the information sheet for the patient. If these elements are not present in the form, the IRB and the regulatory authority would issue a negative statement regarding the study documentation and the trail would not commence.

Informed Consent form - basic components and requirements. ***Preserving individual's dignity and giving the opportunity to make a voluntary decision***

As we have already explained, the Patient Information sheet and Signature page are not only documents to be signed, but above all a process of exchanging information that includes discussion, explanation, questions and answers, and finally – an act of consent, proved by the signatures of the participating parties. The main principles of this process are information, comprehension, and voluntary action.

There are standard requirements for the information provided to participants in clinical trials, which include: objectives of the study, procedures during the trial, risks and anticipated

benefits, possible therapeutic alternatives, and a consent form offering the opportunity to terminate the participation in the trial at any time.

The volume and nature of the information provided to the patient should be sufficient so as to make a decision about participation or refuse participation in a clinical trial. Even if participation in the trial is linked to an immediate benefit, the participant should clearly understand the voluntary nature of participation. Information about existing risks cannot be concealed in order to ensure the cooperation of the participants and direct answers should be given to direct questions about the nature of the trial and the possible risks.

The investigator should make sure that the clinical trial participant has understood the information provided. This can be achieved by asking questions or by asking the participant to describe some of the clinical trial details using his/her own words. It is important to explain to the participant that he/she has the right to ask questions before, during and after the end of the study.

Here are some straightforward recommendations regarding the format of the 'Informed Consent Form' as a document:

- Words must be known to the reader;
- All scientific, medical and legal terms must be explained;
- Information must be provided to the participant in the form of short and concise sentences addressed directly to the participant (maximum of 15 – 17 words in a sentence);
- Use of capital and small letters, lined left and uneven right border of the text etc.

Presented in this way, the document is more comprehensible to the participant and thus secures the premise of his/her active participation in the process of informed consent.

Volunteering

Consent for participation in a clinical trial has value only if it is given on a voluntary basis. This condition requires informed consent, received without coercion or undue influence on the participant. Coercion occurs in instances in which one person intentionally threats another to ensure cooperation. Alternatively, undue influence involves making overtures (clearly formulated or not), creating the expectation of a beneficial outcome (benefit) or

providing other inappropriate assurances in order to obtain consent. The researcher must assure himself that the circumstances in which the informed consent was given did not include coercion or undue influence on the participant. On the other hand, the participants must be clear that they have the right to refuse participation or withdraw from the trial at any time after the start.

Although there is still an ongoing debate regarding the type and volume of information that needs to be provided to the participants to comply with the requirement for informed consent, there is an agreement in relation to the so called *mandatory elements* of this document. Even though each study is unique in its design, the following details must be included in the patient information leaflet:

- Introductory address to the participant (explaining that this is a clinical trial);
- Objectives of the study;
- Description of the study procedures (explaining which are experimental);
- Duration of participation in the study;
- Potential risks and discomforts related to participation;
- Potential benefits from participating;
- Opportunities for alternative treatment;
- Statement about confidentiality of medical data;
- Statement about compensation in case of injury linked to participation in the study;
- Contact details of persons to be contacted in cases of emergency, problems, etc.;
- Voluntary participation consent form.

It is important to include some other pieces of information, if they refer to the specific trial and participants should know about them:

- Information about possible unexpected risks;
- Conditions under which participation is suspended without asking for the patient's consent;
- Additional expenses for participation in the study;
- Consequences of withdrawal from the study (if there are possible effects on the health and welfare of the participant);
- Statement that any newly acquired information that becomes available during the trial will be presented to the participant;
- Anticipated number of study participants (if this can influence the person's desire to participate);
- Payment provided (if any).

Despite the existing clarity about the main principles of informed consent as a process and the general agreement on the volume of information, as well as the form in which it should be presented to the participant, there is still some misunderstanding about the importance of the informed consent.

Myth 1: The informed consent is designed primarily to protect the legal interests of the study team.

Reality: The aim of the process of obtaining informed consent is to protect the participants in the clinical trial by providing access to information, which will enable them to make a voluntary choice.

Myth 2: The investigators expect that the study participant will immediately sign the 'Informed Consent Form'.

Reality: In fact, the larger part of the informed consent process is the discussion with the investigator – before, during and after the end of the trial. The written Informed Consent Form forms the basis of this discussion. It is difficult to envisage how long this process will take but thorough discussion and understanding is beneficial for both sides.

Myth 3: Investigators know better what the patients suffer from and they, rather than the patients themselves, should decide whether or not it is suitable for them to participate in the study.

Reality: Certainly, investigators are a reliable source of advice and information but the patient alone must take the decision to participate. No one – not even the most qualified investigator - can foretell whether the clinical trial will have a beneficial outcome for the participant. The informed consent process is designed to help the participant to weigh the advantages against the risks of participation and to make a personal choice.

Myth 4: Once the participant has signed the consent form he/she must stay in the trial to its end.

Reality: This is not true. Even after the patient has signed the participation document, he/she has the right to change his/her mind at any time and to decide to discontinue participating in the study. Furthermore, the patient has the right to withdraw from the clinical trial at any time and without the obligation to provide any specific reason. And lastly, after exiting the study the patient has the right to continue receiving treatment for his/her condition in line with the established medical practices.

Myth 5: Investigators are very busy people and, therefore, cannot be relied upon to take time to listen to the questions of the patients or to inform them about the course of the study.

Reality: it is the investigator's obligation to inform the study participants, to make sure that they have understood this information and to answer their questions related to the study. Each study participant should be given the name and telephone number of the doctor whom he/she can call to ask questions. It should be remembered that conducting a clinical trial is made possible thanks to the engagement and support of all participants.

Other documents, which might be provided to the patient

Often the investigator asks the study participants to fill in a diary. It is written in a comprehensible language and entails daily recording of the disease symptoms, while the severity of symptoms is defined by the patient by using a number scale (for example a headache: light – 1; moderate – 2; severe – 3). In this way, information about the symptoms and the course of the illness is obtained without the need to maintain daily contact with the participants. Apart from this data, the diary provides the investigator with information about suspected unexpected serious drug reactions. This has important implications for the follow up procedure of drug registration.

The patient diary is presented to the investigator during each visit and, after the completion of the trial it forms a part of the complete study documentation.

With the advances in information technology, the study participants are often asked to 'fill – in' the diary by daily phone call in a system of voice message registration. The only difference is that the questions are pre-recorded and the participant answers by pressing the buttons of the telephone.

Many clinical trials (mainly in phase III) include research of the quality of life as part of the main comparative study within the trial. The research is carried out by filling in a questionnaire, which contains the following groups of questions:

- Related to fulfilling professional duties;
- Related to fulfilling domestic duties;
- Related to general physical state (fatigue, weakness, fitness);
- Related to the emotional condition (anxiety, depression etc.).

Many of the questions may appear strange but this information is necessary to assist the process of developing a new treatment.

Chapter 5

Other Guarantees for the Safety of Study Participants

Role of the IRBs

Before the start a clinical trial at a research center the entire documentation is reviewed and approved or disapproved by an independent expert body – the Institutional Review Board (IRB). Approval by an independent IRB is required before embarking on any clinical trial. All hospitals doing scientific research have their own IRBs, which comprise of:

- Doctors
- Nurses
- Researchers
- Representatives of professional associations
- Representatives of the hospital administration
- Lawyers, journalists, public figures, spiritual leaders

The main task of each IRB is to review and assess the scientific, medical and ethical aspects of the proposed clinical trial and to provide regulatory approval for its conducting. As a rule, when approving a clinical trial, the IRB must determine whether the following requirements have been met:

1) The risks for the participants have been minimized by:
   - Using procedures which are in line with the intentions and do not expose the participants to risks exceeding the necessary ones, and
   - Using procedures, which have already been applied on people for the purposes of diagnosis and treatment (when possible).
2) The risks are acceptable in relation to the anticipated benefits for the participants, if there are any, and in relation to the anticipated knowledge. When assessing the risks and benefits, the IRB takes into consideration only those that derive directly from the clinical trial (by dissociating them from risks and benefits which the participants may experience even if they don't take part in the study).
3) The choice of participants must be impartial. In assessing this criterion, the IRB should take into account the objectives of the study and the environment in which it will be conducted.

4) The informed consent is obtained before any study procedure is performed. Participant's decision must be documented by signing the informed consent form.
5) The clinical trial plan provides opportunities for observing (monitoring) the data collected to guarantee the safety of the participants.
6) There are sufficient mechanisms for protecting the participants' personal data and maintaining the confidential nature of the information.
7) Additional measures are taken to protect the rights and dignity of "vulnerable" participants and to eliminate any possibility for undue influence on them. Representatives of the following groups are classified as vulnerable participants: people in detention, pregnant women, people with physical or mental disability, and representatives of socially and economically disadvantaged ethnic groups.

In addition, the IRB must be convinced that:

- The Principal Investigator (and proposed clinical trial team) are sufficiently qualified and possess the necessary experience to conduct a clinical trial;
- The information provided to the participants is comprehensive and written in a language comprehensible to them;
- The assigner of the study has provided financial compensation in case of health damage connected to participation in the study.

After the initial approval to carry out the study, the IRB continues to supervise it in order to ensure that:

1) The ratio between risk and benefit remains acceptable for the participants;
2) The process of obtaining an informed consent is carried out under the requirements;
3) The inclusion of patients in the trial has been just and impartial.

As part of this ongoing supervision, the IRB continues to receive information about the number of recruited patients and their demographic profile, the adverse events and suspected unexpected serious drug reactions that have occurred, the number of participants who have withdrawn from the study and the reasons for this, the preliminary study results and publications. The study doctor should provide this information to the Institutional Review Board on a regular basis, while after the end of the clinical program the investigator provides a mandatory report with the final data from the clinical center.

Insurance policy

The only possible method of insuring clinical trials is by the policy “Item/Product Liability: as a separate policy or as an addition to an already existing policy “General Liability” covering the activity of the company (public and product liability). The insurance needs to be agreed on the basis of “event occurrence” so that ensuing claims could be related to the period of conducting the clinical trials.

Chapter 6

Control on Clinical Trials

Independent Control Agencies (Regulatory Authorities)

Adhering to the rules of good clinical practice (GCP) is a shared responsibility in the framework of the pharmaceutical industry among the sponsors of clinical trials, Institutional Review Boards, clinical researchers and representatives of the control agencies. In fact, the idea of GCP was born and developed in the USA. This is not accidental – the regulation (control) of drug use in the US dates back to 1913.

At the beginning of the 60s the tragedy involving the drug thalidomide led to increased demand for control over the use and sale of drugs and the conduct of clinical trials both in Europe and the USA. However, it was not until 1977 that the Food and Drug Administration (FDA) in the US first introduced requirements directed at the researchers and sponsors of clinical trials and the IRBs. According to these requirements, only drugs, bio-products and medical products that have been proved to be safe and effective can receive commercial registration. The European Medical Agency (EMEA), which was set up in 1995 as a decentralized body within the European Union has fulfilled a similar role.

The agencies carry out the requirements of GCP by controlling the process of developing new drugs, bio-products and medical products. The control is exercised by reviewing the required reports of the clinical researchers, sponsors and independent ethics committees as well as by programs for inspecting the places where studies take place.

The aim of the inspection is to check whether the rights of the study participants have been protected, as well as to evaluate the quality and completeness of the data collected. Subject to control are: the sponsor of the study, the principal investigator, as well the whole study documentation. Immediate control over clinical research studies is exercised by inspectors appointed by the FDA. It is in their competence to stop a clinical trial until any violations are eliminated or to suspend the study altogether.

Control by the study sponsor

Apart from the control exercised by the state regulatory agencies over clinical trials, the control exercised by the study sponsor is a more rigorous and consistent observation process. It includes continuous assessment (monitoring) or a periodical evaluation (audit) of the study documents and procedures.

GCP demands that the study sponsor should apply and maintain a quality control system in line with devised written standardized operational procedures which should verify that the clinical trial has been conducted and the data has been derived, documented and reported according to the protocol requirements, GCP rules and applicable regulatory requirements.

This system of quality control should be applied at each stage of data collection so as to verify data accuracy and correct processing.

Chapter 7

Assessment of Risks and Benefits

The safety of the study participants and the provisions for their best treatment are the most significant demands of contemporary clinical trials, based on the Declaration form Helsinki, 1964.

The crucial point when taking a decision for or against participation in a trial is the assessment of potential *benefits* and *risks*. These terms are closely related to other two principles – this of *"making good"* and that of *minimizing the risks,* as reflected by the ancient medical edict "Primum non nocere", i.e. no harm to the patient.

The start of a research study is preceded by an assessment of the potential risks and benefits. They become the basis of the IRB's assessment whether a research trial has sufficient ethical and medical grounds to proceed. These fundamental principles of ethical judgment were published in a separate report in 1979 and the US FDA (Food and Drug Administration) used them as the basis to develop a control system for clinical trials. It is known as "The Belmont Report" named after the chairman of the Senate Committee, investigating the problem. There are three fundamental ethical principles in the Belmont Report:

- An Individual's independence or respect for the decision of the person;
- Efforts to secure the well-being of the individual;
- Equal approach to all participants in a research trial.

Although it is not stated as a fourth separate principle, there is reference to "doing no harm" in the text of the report.

Thus, reviewing and judging by these principles helps both the Independent Institutional Review Boards (IRBs) and the patients to make their assessment. A key point in conducting clinical trials is the establishment of such IRBs. They are independent bodies, established at a hospital, whose members are experts in different medical specialties as well as people who are not working in the hospital and non-medical persons (laymen). The functions and responsibilities of IRBs are determined concisely by the International Harmonization Conference and detailed as "independent bodies…, whose objective is to safeguard the rights, safety and well-being of all trial subjects."

Potential Risks

There are different types of risks for a clinical trial subject, even if the principle of "doing no harm" is applied extremely conscientiously. The harm is not necessarily a result of purposeful, ill-minded acts; it might happen involuntarily and it might even be the result of good intentions. We shall try to present here some groups of risks that are relevant not only to the field of clinical trials so that they could be identified and avoided whenever possible. Attention should be drawn to: physical, psychological (emotional), social (the most frequent here being the stigmatization of the participant, i.e. the attitude towards him to change, as a result of loss of confidentiality), economic and legal risks – all possible aspects of a clinical trial that might have certain effect on the participant are included here.

Potential Benefits

The word "benefit" may be defined as "a favorable factor or condition, advantage, profit". Generally it is hard to apply this definition directly to the participants' expectations of a clinical trial. A patient who accepts the terms of participation thinking of a benefit or personal profit might have very unrealistic expectations. The answer is hidden in the definition of research work that is usually represented as "working for development or contribution to overall knowledge". Consequently, a fundamental purpose of any research is to investigate or to create knowledge that will benefit society in the future. The fact that many drugs widely distributed and used in contemporary medical practice have never been investigated in such details as we do today should not be forgotten. A patient cannot expect 100-percent-guarantees, yet the concomitant benefits together with the possible direct ones finally result in an overall positive effect arising from voluntary participation.

Direct benefits for every patient could be:

- access to the best treatment available so far;
- access to examination by leading specialists in the particular medical field;
- early and comprehensive diagnostics, which might result in detecting a certain new pathology unknown so far;
- chances of effective impact on the disease;
- regular and detailed observation done by medical specialists.

In conclusion it can be stated that accepting an alternative way of treatment or the best known method so far, combined with strict observation of a patient leads to

improvement of the overall health condition. Clinical trials contribute to development of society through investment in the field of health protection and establishing new job positions for highly qualified staff.

Society benefits from clinical research through the development of new medications and new ways of treatment based on the results from clinical trials. In Western Europe and North America patients have unlimited access to various sources of information and modern technologies thus having the opportunity to apply the best treatment for their disease.

The overall process of a clinical trial and the anticipated benefits are described correctly in the Informed Consent Forms, so that study participants got to know them on enrolling into the study. In cases where the participants do not understand the essence of the clinical trial process, the investigator should explain them all phases and details of the clinical study, as well as with all aspects of the research process thus allowing the patient to make a balanced and adequate decision.

Chapter 8

Some Considerations When Making a Decision For or Against Participation in a Clinical Trial

Without doubt clinical trials are the most plausible source of reliable information about drugs and treatments' efficacy, especially when comparing methods of treatment with moderate effect. Without these trials there is a risk that ineffective or even harmful therapeutic schemes and interventions might find place among the modern standards of medical practice. Unfortunately still a large part of medical practice is not based on the so called '***medicine of evidence'*** because of the fact that findings are either overlooked in a light-handed manner at the background of existing 'standards' or considered inapplicable on patients existing in reality or are lacking altogether.

We must confess that not all clinical trials have a design, which allows application of their results (in case they are positive) in real medical practice. Therefore, apart from the direct results, which are usually linked to the efficacy of treatment of a particular disease, there are other criteria that matter for every patient. They are usually represented by other two main categories – improved quality of life and decreased unpleasant and sometimes life threatening unwanted side effects.

From everything mentioned so far it becomes clear that there isn't one single answer, a universal key to solving the difficult question arising in front of each patient who has been offered to participate in a clinical trial – TO BECOME OR NOT TO BECOME A STUDY PARTCIPANT? The answer is always exclusively personal; however we'll allow ourselves to summarize in brief the most important points that must be considered by the patient in such cases.

In the first place each patient must have at his/her disposal sufficient data and time for considering his/her participation. He/she could find most of the answers in the main document that every participant receives- the Patient Information sheet. It contains information on the research design and objectives, whether these objectives are applicable in real medicine, on real patients and whether the research plan has been coordinated with the main medical therapy accepted as a standard in the medical practice.

Secondly, do the patients sought after for participation exist as a real group in the daily medical practice or are they artificially selected to achieve the aims of the study?

And finally – what is the preliminary assessment of the *'benefit/risk'* ratio confronting the participants in the new therapeutic scheme or intervention? It is normal practice to provide data from previous studies, which have served as a basis for commencing the current study. They offer accumulated experience both in relation to the efficacy of the treatment offered and to the risks from unwanted events. Very rarely, usually in pilot trials in phase I and II we do not have such data available, but in these cases normally your participation has been preceded by that of healthy volunteers under the devised study design.

Once again we would like to point out that the right answer has not been written down in advance. The right answer is the one, which most fully coincides with your anticipation or desire to participate in a research trial. With the current information we are only trying to assist the future participants in their choice. For this purpose it is necessary to focus your attention on the following two key points:

Point 1: When you ponder over the question of participating in a study, find out what its main alternatives are – what is the standard therapy applied in the practice of the research doctor who offers you participation?

Point 2: Make sure that you have understood correctly by what your participation in a trial would differ from what is offered to you as a standard therapy. Make sure you have understood how the risks would be different, how the benefits would be different and what different procedures there are on offer.

Focusing on these points will help you make an informed choice between the opportunities offered.

Appendix 1

Glossary

Adverse event, serious adverse event and serious adverse reaction

An adverse event is each unfavorable change in the patient's health when using prescribed medication. This change may not necessarily be linked to the treatment.

A serious adverse event is an unfavorable medical incident, which (irrespective of the dose of drug) has caused:

- Death;
- Immediate life threat;
- Hospitalization (or increasing the period of preceding hospitalization);
- Serious or permanent damage or invalidity;
- Considerable medical event;
- Congenital disorder.

Placebo

A Placebo can be defined as a 'false' drug that contains only an inactive, harmless substance (starch or artificial sweetener). It looks like the study drug – the same form and color of the tablets, the same size of ampoule. This prevents the clinical trial participants from being pre-conditioned. The placebo-therapy, in combination with randomization of trial participants, is a powerful tool for eliminating pre-conditioning and obtaining verifiable data about the efficacy and safety of the investigational drug.

'Blinding' the trials

A 'Single-blinded' trial is a clinical study where only the participants are unaware of what medication exactly they are taking – the study drug, standard treatment or placebo. Each participant receives exactly the same injections or tablets so that he/she cannot tell the difference. Unlike the patients during the trial, the investigator knows who gets what.

A 'double-blind' or 'double-blurred' trial is a research study in which the investigators do not know what medication they give, and the participants do not know what they receive. The medication package has been marked in advance with code numbers and supplied directly to the investigator. There is no way of finding out which package contains what drug. The same applies to the participants in the clinical trial.

However, in order to guarantee the safety of the participants, there is always a procedure in place allowing identification of what a particular study participant has been taking. This procedure is called 'unblinding' or 'unmasking' of the code and it is responsibility of the research team. In most instances it is the abrupt deterioration of a trial participant's health that reveals the absolute need to break the code, especially if an antidote is needed against the effects of the taken substance. In practice, this is done by opening an envelope containing the necessary information.

Randomization

The term has been generated from the English word 'random' (= accidental, arbitrary) and means division of clinical trial participants into groups on an arbitrary basis. One of the groups receives the study drug, the other one – the standard treatment, placebo or no treatment (see above). It is possible that the patients from the study drug group are additionally randomized with regard to the dosage. Often this group is called 'the experimental' group. Patients receiving the standard treatment (the type of treatment they would receive for their condition if they were not participating in the trial), placebo or no treatment at all form the so-called 'control' group. In these instances the clinical trial is called a 'randomized control trial'.

Pure randomization is achieved by using powerful computers in which the drug batch numbers produced for use during the trial have been entered in advance. During randomization (which is mostly done over the phone) the investigator 'draws' the batch number from the computer memory and supplies the participant with a batch with the same number.

Appendix 2

WORLD MEDICAL ASSOCIATION (WMA)
HELSINKI DECLARATION

Ethical principles of medical trials involving people

Adopted at the 18-th General Assembly of WMA, Helsinki, Finland, June 1964 and extended by the 29-th General Assembly of WMA, Tokyo, Japan, October 1975, 35-th General Assembly of WMA, Venice, Italy, October 1983, 41-st General Assembly of WMA, Hong Kong, September 1989 and **48-th General Assembly of WMA, Somerset West, South African Republic, October 1996 and** 52-nd General Assembly of the WMA, Edinburgh, Scotland, October 2000

- **INTRODUCTION**

1) The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on 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 will 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 research that ultimately must rest in part on experimentation involving human subjects.

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

6) The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously

be challenged through research for their effectiveness, efficiency, accessibility and quality.

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

8) Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and require 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 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) Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects stated in this Declaration.

- BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving 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 ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

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

15. Medical research involving human subjects should be conducted only by 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.

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

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should end any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving 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.

19. 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.

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

21. The right of 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.

22. In any research on 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 participation in the study or to withdraw consent to participate at any time without repercussions. 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.

23. 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.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. 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. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for 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 authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

B. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. 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 placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. 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.

31. 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.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.