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NAWA NARODOWA AGENCJA WYMIANY AKADEMICKIEJ

Legal regulations in clinical trials

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Legal regulations of clinical trials

1. The regulations and control of clinical trials in Poland.
2. International regulations of clinical trials.
3. Institutions supervising the conduct of clinical trials in Poland.

The regulations and control of clinical trials in Poland.

1. Pharmaceutical law dated 6.09. 2001 (Journal of Laws 2001 no. 126 item 1381)

- Defines the term clinical trial which is any study carried out on people

in order to discover or confirm the clinical and pharmaceutical, including pharmacodynamic, effects of one or more medical products under study , or to identify the adverse effects of one or more of the medical products under study, or to track the absorption, distribution, metabolization, and excretion of one or more of the medical products under study, taking into consideration how safe and effective they are.

- It defines the term of Good Clinical Practice - as a set of requirements acknowledged by the international community in regard to the ethics and quality of scientific research when conducting clinical trials, which guarantee the protection of rights, the safety, and the welfare of the participants of such studies, and the credibility of their results;

The regulations and control of clinical trials in Poland.

1. Pharmaceutical law dated 6.09. 2001 (Journal of Laws 2001 no. 126 item 1381)

- Regulates the requirements of conducting clinical trials.
- Each clinical trial may be conducted only on the basis of a previously issued permit by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, as well as a positive opinion of a bioethics committee.
- The President of the Office enters the clinical trial into the Central Registry of Clinical Trials.

- In accordance with the act of Pharmaceutical Law, the clinical trial of a medicinal product under study is carried out in accordance with the Good Clinical Practice which ensures a standard defining the way clinical trials are planned, conducted, monitored, documented, and their results reported, when people are involved in the study.

2. Good clinical practice

- The decree of the Minister of Health dated 02.05.2012 regarding Good Clinical Practice.

- The document defines the conditions for a clinical trial:

§ 3. A clinical trial must be:

1) justified by pre-clinical trial results and, if applicable, by data gathered from prior clinical trials of the medicinal product under study;

2) justified scientifically and described in the clinical trial protocol;

3) based on ethical rules;

4) conducted by people who are qualified enough in their profession, have the necessary scientific knowledge and experience when working with patients, necessary to conduct a clinical trial, and that guarantee its proper quality;

5) conducted in a research facility.

- The document regulates the duties of a researcher and a sponsor within the confines of the clinical trial being carried out. It determines the rules of creating a clinical trial protocol, a researcher's brochure, and the contract for carrying out clinical trials.

3. Clinical trials involving minors

- This is regulated by the Decree of the Minister of Health dated 30.04.2004 on the means of conducting clinical trials involving minors. Before making a decision to start a clinical trial involving minors one should conduct analysis of the necessity to carry out such trials.

§ 1.

Before making a decision to start a clinical trial involving minors one should conduct analysis of the necessity to carry out such trials, where the following should be particularly considered:

1) the frequency of occurrence of a disease, where the medicinal product is to be used for treatment;
2) the level of intensity (seriousness) of the disease being treated;
3) the availability and convenience of existing alternative means of treatment, considering their effectiveness, the profile of side effects, including the peculiar problems of safety connected with using the medicinal product for minors;
4) the originality of the medicinal product;
5) the scope of recommendations;
6) the necessity of establishing special termination points other than those specified in the clinical
trials in adults;
7) the necessity to separate into age groups for which the medicinal product is to be used;
8) the existence of special issues related to the safety of medicine meant for minors with consideration of all the safety problems indicated by the pre-clinical trials;
9) the necessity to create a special paediatric form of the medicinal product;
10) the existence of the possibility of a significantly advantageous new method of treatment using the new medicinal product over hitherto known methods of treatment of serious life-threatening diseases.

4. The Act on the professions of doctor and dentist

- The clinical trial can only be performed by doctors. In accordance with the Act on the professions of doctor and dentist, dated 05.12.1996, the following are also considered as performing the job of a doctor: conducting research in the field of medical sciences or health promotion, and teaching the profession of doctor.

2. Supervision of the conduct of clinical trials

- In accordance with the regulations of the Pharmaceutical Law, supervision of the conduct of clinical trials is done by the **President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products**.
- To improve the President's work, the **Department of Medicinal Products Inspections** was created in 2011. Inspections may be carried out in a national mode and as a task from the European Medicines Agency. Inspection may concern the facility, the registered office of the sponsor, the organisation conducting the clinical trial as part of a contract (CRO), or other places deemed necessary. The mode and detailed scope of carrying out the inspection of clinical trials is defined by the Decree of the Minister of Health dated 26.04.2012 on the Inspection of clinical trials.

Central Registry of Clinical Trials

- The Central Registry of Clinical Trials is a data registry kept as an IT system by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products.
- Information on any new registered clinical trial is input into the CRCT.

The CRCT registry holds:

- the title of the clinical trial;
- the number of the clinical trial's protocol;
- the number of the clinical trial in the European database for clinical trials (EudraCT);
- the names and addresses of the research facilities where the clinical trial is held;
- the phase of the clinical trial;
- the name of the medicinal product under study;
- the name of the active substance;
- the number of the participants of the clinical trial;
- the characteristics of the groups of participants in the clinical trial;
- the first name, surname, and place of residence, or the name and registered office of the sponsor;
- the first name, surname, and academic title and degree of the researcher;
- the first name, surname, and academic title and degree of the coordinator of the clinical trial, if present in such a trial;
- the date of filing for the clinical trial;
- the date the clinical trial ends;
- information on the decision regarding the clinical trial;
- the number of the clinical trial in the Central Registry of Clinical Trials.

Third-party liability insurance of the researcher and the sponsor:

- The sponsor and the researcher are held liable for conducting the clinical trial.
- The requirement to conduct a clinical trial is to have the sponsor and researcher sign a third-party liability insurance contract.
- The minimum guaranteed sums of a third-party liability insurance are defined by the Decree of the Minister of Finance, dated 30.04.2004, regarding the compulsory third-party liability insurance of the researcher and sponsor.
- The minimum guaranteed sum of a third-party liability insurance depends on the number of people participating in the clinical trial.

Third-party liability insurance of the researcher and the sponsor

At present the guaranteed sums are:

- 500.000 Euro - if up to 10 people take part in the trial;
- 1.000.000 Euro - if 11 to 25 people take part in the trial;
- 2.000.000 Euro - if 26 to 50 people take part in the trial;
- 4.000.000 Euro - if 51 to 100 people take part in the trial;
- 5.000.000 Euro - if over 100 people take part in the trial.

- The above sums are the same for a single and all events covered by the insurance during a given insurance period

International regulations of clinical trials

1. **The Nuremberg Code** (end of World War II)

➢ the first regulation of the most important areas related to conducting clinical trials, including the following:

- the obligation to receive a conscious agreement from the patient
- indicating the benefits of the trial
- the right for the patient to back out of the trial at any moment
- the obligation for the one conducting the trials to limit the risk and the requirement to stop the trial should there be a threat to the participants.

➢ According to the Nuremberg Code, only people able to sign a legal agreement could participate in a clinical trial, which excluded children and incapacitated persons.

International regulations in clinical trials, continued

2. **Declaration of Helsinki**
(published in 1964 by the World Medical Association).

- modified multiple times, most recently in 2008.
- it regulates:
  - the subject of the trial itself, which must have a scientific basis, and if possible should be preceded by clinical trials on animals.
  - the rights and obligations of the patient, the researcher, and the sponsor:
  - the participant of the trial should be informed about the aim, the method, the risk, and the potential benefits from the trial, and in order to take part in the trial, they should sign a written agreement.
  - the researcher is obligated to have the required qualifications.
  - both the researcher and the sponsor are responsible for the safety of the patient during the trial.

- There should exist a protocol of the trial, approved by an independent ethics committee.

3. Laws regulating the drugs market (USA)

- The first legal regulations regarding the drugs market appeared in 1927 in the USA, when the FDA (Food and Drug Administration) was created to oversee compliance with the chemical purity of drugs and the correctness of the information on the labels.
- Today, clinical trials in the USA have to be conducted in accordance with the regulations present in the Code of Federal Regulations of that government agency, which registers drugs in the USA.

International regulations in clinical trials, continued

4. European Union Regulations:

4.1. The Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The assumptions of the Directive 2001/20/EC of the European Parliament and of the Council

- all clinical trials must be planned in accordance with the GCP *(Good Clinical Practice) rules*
- clinical trials can only be conducted when the benefits for the patient or the society outweigh the risk and inconveniences which may be a threat to the patient
- a conscious agreement to participate in the trial needs to be given in written form, dated and signed (illiterate people may do this orally, which must be confirmed by a witness in writing). In cases of people legally unable to provide a conscious agreement, the agreement needs to be made by a legal representative, but only in case of trials which benefit the participant
- in cases of trials involving minors the child's agreement is required (if they are able to understand the situation), as well as that of the parents or a legal representative

The assumptions of the Directive 2001/20/EC of the European Parliament and of the Council

- in trials involving minors, one must minimise the pain, discomfort, or fear of the participant, and the ethical committee which gives the opinion should include a paediatrician or consult a paediatrician for their opinion
- defined the concepts of SAE – Serious Adverse Event, and SUSAR – Suspected Unexpected Serious Adverse Reactions;
- the European database for clinical trials (EUDRACT) was created
- requirements for the labels of medicinal products under study were put in place.

International regulations in clinical trials, continued

4.2. Directive 2005/28/EC of 08.04.2005 of the Commission:

- regulates the implementation of the detailed guidelines for GCP under the European legal system, and defines the requirements for authorisation of the manufacturing or importation of the medicinal products under study, and defines the detailed guidelines for documenting clinical trials, archiving the documents, the qualifications required of the inspectors, and the supervision procedures.

International regulations in clinical trials, continued

4.3. Directive 2003/94/EC of the Commission on Good Manufacturing Practice

4.4. Directive 95/46/EC of the European Parliament

and of the Council on the protection of individuals

4.5. There are additional regulations in place on reporting data related to the safety of the medicinal products under study and regulations related to the use of genetically modified organisms.

International regulations in clinical trials, continued

4.6. Regulations:

4.6.1. Regulation 536/2014 of 16.04.2014 of the European Parliament and of the (EU) Council on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC.

Which institutions supervise conducting clinical trials in Poland

The President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, and the **Chief Pharmaceutical Inspector** are the most important institutions responsible for the proper conduct of clinical trials in Poland.

Each clinical trial in Poland, before it starts, must be accepted by these two institutions. They are:

- The President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
- An Independent Bioethics Committee

Additionally, these authorities supervise the trial during its span and after it ends.

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The President of the Office for Registration of Medicinal Products

- The President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, The President of the ORMP for short, who reports directly to the Minister of Health, supervises the correctness of the conduct of clinical trials in Poland.
- The main task of the Office is to issue consent for starting a clinical trial, in accordance with the regulations in place, and to control if the rights, safety, health, and welfare of the participants of the clinical trial are respected.
- Supervision over the trial is done by an internal authority of the Office - the Inspectors of Clinical Trials, who can conduct an inspection at the research facility, at the place of residence of the sponsor of the trial, or at the registered office of the CRO, at any time.

Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych

Działając w obszarach produktów leczniczych, wyrobów medycznych i produktów biobójczych chronimy zdrowie i dbamy o bezpieczeństwo społeczeństwa.

The President of the Office for Registration of Medicinal Products

In accordance with the regulations of the Pharmaceutical Law, supervision of the conduct of clinical trials is done by the President of ORMP (the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products). The scope of the competencies for the President is defined in the act on the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, dated 18.03.2011. The President supervises the trials with the help of the Inspectors of Clinical Trials.

As part of their competencies, the Inspectors of Clinical Trials undertake actions aiming to check the following:

- if the clinical trial is conducted based on a consent issued by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products,
- if the requirements of the consent are adhered to;
- if during the clinical trial the entities participating in the trial are adhering to the obligations stemming from the requirements of Good Clinical Practice;
- that the participants of the clinical trial have handed in the forms of informed consent;
- that an opinion of a bioethics committee has been obtained, mentioned in the act of 06.09.2001 - the Pharmaceutical Law;
- the rooms and equipment used in the clinical trial;
- adherence of the conduct of the clinical trial to the protocol of the clinical trial and the accepted changes to said protocol;
- the means of documenting data and storing the documentation;
- if the post-inspection recommendations were implemented.

In terms of the supervision competencies of the President of the Office over the conducted clinical trial, one should consider that if there exists a justified suspicion that the requirements based on which the consent was given are not being met any more, or the gathered information justifies the doubts regarding the safety or scientific relevance of the ongoing clinical trial, or there is suspicion that the sponsor, researcher, or other person participating in conducting the clinical trial have stopped adhering to the obligations placed upon them, the President of the Office can make one of the following decisions:

1) order the removal of the omissions within a given time or
2) suspend the clinical trial or
3) withdraw the permission to conduct the clinical trial

Should any abnormalities or omissions be stated, and documented in the inspection report, the President of the Office delivers the sponsor and the researcher a report with a motion to remove the abnormalities and omissions within no longer than 30 days from having received the report. The sponsor and the researcher inform the President of the Office immediately about having carried out the post-inspection recommendations or about the reasons for being unable to do so.

Similarly, if after the clinical trial has concluded, including due to an inspection of the clinical trial, there exists a warranted suspicion that the requirements, based on which the permit for conducting the clinical trial was issued, were not met, or the application for marketing authorization for the medicinal product and the documentation attached to it were not presented reliably, the President of the Office issues a decision to:
forbid using the data the reliability of which was questioned, including the removal of such data from the documentation which is the basis for issuing a permit authorising the marketing of the medicinal product, or withdraw the permit allowing the sale of the medicinal product

Abnormalities found as part of a Clinical Trial Inspection can also result in criminal liability. Anyone who conducts a clinical trial without the required permission or in violation of the provisions of the Pharmaceutical Law shall be subject to a fine, restriction of liberty, or imprisonment for up to 2 years

Chief Pharmaceutical Inspector

Supervision over hospital pharmacies, including that of their participation in clinical trials, in terms of storing the medicinal product under study falls under the competencies of the CPI (Chief Pharmaceutical Inspector).

GŁÓWNY INSPEKTORAT FARMACEUTYCZNY

Patient Rights Ombudsman

As part of a clinical trial, the participant of such a trial, the patient, receives healthcare services. As part of the process of providing healthcare services, the patient has certain rights, described in the act of 06.11.2008 on Patient Rights and the Patient Rights Ombudsman.

One of the primary competencies of the Patient Rights Ombudsman is to initiate explanatory proceedings in case they become aware of a violation of patient rights.

Biuro Rzecznika Praw Pacjenta

What role does the Bioethics Committee play?

The Bioethics Committee assesses if ethical and scientific standards have been met by the proposed clinical trial. The members of the committee are fully independent of the company sponsoring the trial. The committee includes, apart from doctors, representatives of other professions, for example a priest, a nurse, or a lawyer. Starting a trial is only possible after having received a positive opinion from the proper Bioethics Committee.

A Bioethics Committee pays special attention to the following:

the contents of the information provided to the patient and the language in which that information is presented, the justification for conducting the clinical trial, its scientific value, the qualifications and the experience of the doctor leading the trial and that of their team, the quality of the facility (hospital, or clinic) where the trial will be conducted, the sum of the insurance or compensation for the patient, the sum of the salary of the doctor leading the trial and their team, and the insurance of the trial.

A PATIENT'S INFORMED CONSENT

What does the abbreviation ICF mean in clinical trials?

ICF is the patient's conscious agreement to participate in the clinical trial. The abbreviation stands for Informed Consent Form. A patient, by signing the form of informed consent, makes a free-will, thought-through, and conscious decision to participate in the clinical trial. Before coming to a decision about participation in the trial, the Patient has the right to ask questions, and be given comprehensive answers and explanations by the doctor. Furthermore, the Patient must have enough time to familiarize themselves with all information regarding the trial (its nature, the character and aim of the clinical trial, and the treatment used in the clinical trial), and with the informed consent form. The Patient also has the right to receive a written copy of the information about the trial and a signed document of consent to participate in the trial, with their signature and that of the doctor. At each stage of the clinical trial, the Patient has the right to back out of the trial. They suffer no consequences by doing so, nor incur any fines.

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