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EU REGULATIONS

DIRECTIVE 2001/20/EC RELATING TO THE IMPLEMENTATION OF GOOD CLINICAL PRACTICE IN THE CONDUCT OF CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE[2]

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 (hereinafter: Directive) was published in the Official Journal of the European Union no. 121 of 1 May 2001. The Directive entered into force on the date of its publication in the EU Official Journal. The EU Member States had the deadline to adopt the laws and other regulations until 1 May 2003, and meet the implementation deadline of 1 May 2004. Based on the provisions of the Directive, Serbia adopted the first Law on Medicinal Products and Medical Devices in mid-2004 - LoMPMD 2004, *Official Gazette of RS*, no. 84/2004, despite not being an EU member state. Truth be told, some of the provisions of the Directive later underwent slight amendments under Regulation no. 1901/2006 of 27 December 2006 and Regulation no. 596/2009 of 18 July 2009. In accordance with the Directive, the effective Law on Medicinal Products and Medical Devices was passed - LoMPMD 2010, Official Gazette of RS, 30/2010, 107/2012, 105/2017-other law, 113/2017-other law.

1. The subject of the Directive are provisions of good clinical practice for the conduct of clinical trials of medicinal products for human use. According to the Directive, good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human su-

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

bjects. Naturally, the Directive does not particularly elaborate on the expression *internationally recognised ethical and scientific quality requirements*.

Such requirements are known from international medical and pharmaceutical conferences and gatherings, as well as from the medical law literature on the international ethical and scientific standards.[3] These standards did not require ratification in national legislations. A number of standards, defined in the process of drafting the Declaration of Helsinki, have met with mixed acceptance since the original 1996 Declaration. Namely, some were supported whereas some were challenged. This is pointed out because the Directive obviously sought to be neutral in relation to the different positions regarding requirements that emerged after the 1996 Helsinki Declaration. Thus, the Directive stresses that such compliance with standards assure that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. Finally, the Directive defines clinical trial as any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

2. No clinical trial in human medicine may begin or end without an investigator and subjects. As a compulsory participant of a clinical trial, investigator may be either principal investigator or an investigator, namely, one of the team members with the special task within the team (investigator-pharmacist, investigator-physician, statistician etc.). According to the Directive, investigator is a doctor or a person following a profession agreed in the Member State for investigations (e.g. M.Sc. in pharmacy, doctor-dentist, biochemist, nurse etc.). Principal investigator is responsible for one trial site and where there is a larger number of subjects or trial

[3] Internationally recognised ethical and scientific requirements are notably the Nuremberg Code and the Declaration of Helsinki. Nuremberg Code was drafted in 1946. After World War II, a series of trials were held to hold members of the Nazi commanders responsible for war crimes, among which there were doctors as well. These proceedings became known as the Nuremberg trials. In that trial, in the part of the indictment against Nazi doctors, one of the prosecutors (Robert Jackson) formulated ten principles according to which medical examinations on people were supposed to be performed, but they were not actually performed, so the doctors were tried for the intention. Soon, these principles were dubbed the Nuremberg Code and accepted in comparative medical and pharmaceutical law. Extending that code, the World Health Organization adopted ethical and scientific standards on clinical trials at an international conference in Helsinki in 1996. Since then, under the name of the Declaration of Helsinki, international conferences have been held in different cities and at different times. The original text of the Declaration of Helsinki was revised several times at international conferences (1975, 1983, 1989, 2000, 2004, 2008, 2013 and 2015). For more details, see Professor Dragica Živojinović, PhD: Historical Development and International Regulations of Clinical Research Involving Human Subjects, *Proceedings of the Faculty of Law in Kragujevac* (2012),677–697.

sites, the principal investigator chooses the appropriate number of investigators and subjects who participate in the trial. Principal investigator directly selects trial sites and collaborators, including supporting staff who participate in the clinical trials. In any case, the Directive treats the principal investigator as a person responsible for one or more trial sites in a particular clinical trial, since clinical trials are usually conducted in more than one countries and in a longer period of time.

3. Another compulsory participant of a clinical trial is a subject. There are several categories of subjects. The Directive defines the subject as an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control. According to the wording of the Directive, these are two main subject categories, whereas the other categories will be mentioned in items 4 and 5. Naturally, the Directive uses a narrative description of the clinical trial procedure, not a manner of setting standards. This means that the Directive does not explain to the reader (Member State legislator) the difference between a subject who, in a trial, receives a medicinal product and a subject who is only a member of the control group for an investigational medicinal product but does not actually receive the investigational medicinal product. In the first case, for investigation is selected an ill individual, who had previously given informed consent to be examined. Informed consent will be explained below in more detail. In the second case, it is a placebo, for which the subject also gave prior informed consent. There is an extensive medical literature on the concept of placebo. The literature primarily discusses the question of the ethics of placebo in clinical trials. In the clinical trial, the principal investigator knows who the chosen placebo investigator is and keeps this information a secret, just as all other members of the investigating team have the duty of confidentiality if they accidentally come across this or other confidential information of the trial. From a purely medical perspective, the placebo subject does not know that he will receive a placebo, and shows an effect during a clinical trial based on suggestibility, because he thinks he is receiving the drug as therapy, while his "drug" is actually empty.[4] The directive also explicitly mentions placebo, regulating the components of the term - the investigational medicinal product - through various pharmaceutical forms of the medicinal product. Thus, in relation to clinical trials, placebo is not exclusively a term from the point of view of medical or pharmaceutical learning (theory), but it is a medical and pharmaceutical legal term within clinical trials provided for and established by the Directive in relation to the pharmaceutical form of the investigational medicinal product.

4. In addition to the two categories of the subjects described above, for the next two categories of subjects, the Directive prescribed *prior informed consent* as a

[4] Professor Zorana Vasiljević, MD Institute for Cardiovascular Diseases KCS Beograd: „Placebo u kliničkim ispitivanjima lekova", *Proceedings of Serbian Medical Society* (2010)

form of voluntary and signed consent to participate in a clinical trial. According to the Directive, an informed consent is a written material, dated and signed, which presents the nature, significance, implications and risks assumed by the insured who affixes his/her signature thereon. If the insured concerned is unable or incapable of signing the consent, he receives the content of such consent orally, in the presence of a witness. The provisions of the Directive explain in more detail how informed consent is obtained for minors and incapacitated adults not able to give informed legal consent. For minors, the Directive envisages that informed consent is obtained from parents or a legal representative. The Directive stipulates that persons with experience in working with minors participate in the obtaining of informed consent, as well as that the principal investigator, in cooperation with the team of investigators, considers whether there is the explicit wish of an (ill) minor to refuse participation or to be withdrawn from the clinical trial at any time. As regards informed consent, the Directive envisages that the minor receives compensation, but no further incentives or financial inducements for participation in a clinical trial. Additionally, within the informed consent, the Directive has tasked the investigating team with informing the minor that some direct benefits are obtained from the clinical trial and that such research should relate directly to a clinical condition from which the minor concerned suffers. The Directive stipulates that clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, as well as the whole set of risks of side effects. The Directive requires constant supervision by a team of investigators for clinical trials in which a minor participates, as well as compliance with the current instructions of the body responsible for medicinal products. Finally, in the case of a minor subject in a clinical trial, the Directive envisages that the expert opinion (favourable or unfavourable) for the trial should be given by an Ethics Committee composed of paediatricians. Thus, the Directive advocates that the interests of the minor participating in a clinical trial always prevail over those of science and society.

5. The Directive more or less repeated the above rules that apply to a minor participant in a clinical trial when adults not able to give informed legal consent are concerned, but with some adjustments to adults. For an adult not able to give informed consent, the informed consent of the legal representative will be obtained if such an adult did not refuse to give informed consent before the onset of his or her incapacity. Further, such persons will receive information according to their capacity of understanding regarding the trial, the risks and the benefits. According to the Directive, such adult will receive compensation but, just like a minor, will not be entitled to any incentives or financial inducements. The Directive envisages that the Ethics Committee shall give its opinion (favourable or unfavourable), and that such Committee shall be composed of the experts in the subject disease and patient population, taking into account clinical, ethic and psycho-social issues of

such patient population. As opposed to participation of minor subjects, for adult individuals the Directive provided for the rule that medicinal products for trial may be administered to all such individuals when there are grounds for assuming that the direct benefit to the patient outweighs the risks.

6. A clinical trial cannot be conducted without an ensured source of funding. In this regard, the Directive indicates the following organisational and legal forms where a financial source for a clinical trial may appear. These are notably individuals (natural persons), companies, institutions and organisations. For quite practical reasons, the mentioned organisational and legal forms are listed in the Directive (English version) under the common name – sponsor of clinical trials. In Serbia, the same solution for different organisational and legal forms was adopted in the effective 2010 LoMPMD. In Serbia, the term *sponsor of clinical trials* in Serbian medical law relates to clinical trials that are exclusively sponsored from abroad.[5] According to the Serbian press, about 1,000 clinical trials are conducted in the EU annually, and up to 100 clinical trials in Serbia.[6]

7. In connection with the conduct of clinical trials in the EU Member State, the Directive envisages the competent authority and the Ethics Committee. The sponsor is required to submit a request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial. The competent authority of the state, before deciding on the merits of the sponsor's request, obtains the opinion of the Ethics Committee. The same procedure applies in the case of an amendment during the conduct of a clinical trial, as well as at the end, when the sponsor of the study is required to submit a report on the completed clinical trial. When medical and legal views are compared, for examination, the Ethics Committee may be organized at the level of a health institution, region or a state.[7] Regardless of its level of organisation, the Ethics Committee is conceived by the Directive as an expert body tasked with giving a favourable or unfavourable opinion on the sponsor's request regarding a clinical trial and submitting the opinion to the competent state authority. Regarding the request for approval of a clinical trial, the Directive obliged the Ethics Committee to first consider the expected benefits and risks, particularly regarding the justification of the clinical trial. The next task of the Ethics Committee provided for in the Directive implies its obligation to consider whether the request for a clinical trial envisages the right of the subject to withdraw from the trial i.e. revoke his or her informed consent without any harmful consequences. The Directive authorised the Ethics Committee to consider how the

[5] Professor Dragica Živojinović, PhD: Ethical Dilemma of Globalization of Clinical Research, *Legal Life* no. 9/2012, 538.

[6] Danijela Davidov Kesar: „Savremena terapija za pacijente uz pomoć kliničkih studija", *Politika,* 5. April 2018,13.

[7] Dr Hajrija Mujović Zornić: „Pravni aspekti rada Etičkih komiteta u medicini", *Legal Life* no. 9/2007,259

clinical trial is planned to be conducted, namely, whether the clinical trial protocol is adequate to the initial requirement. With regard to the requirement for clinical trials, the Directive drew particular attention of the Ethics Committee to the issue of providing insurance or indemnity to cover the liability of the investigator and sponsor. Moreover, during the conduct of a clinical trial, the Directive obliged the Ethics Committee to provide opinion on the following set of issues: whether the subjects received compensation; whether indemnities were paid in the event of subjects injury or death attributable to a clinical trial; whether investigators or subjects received any rewards and finally, whether healthcare institutions receive any compensation in accordance with the agreements for clinical trial concluded by the sponsor? In practice, the above provisions of the Directive are understood in most EU Member States as a recommendation or even as a legal basis to introduce compulsory insurance or a bank guarantee as a cover for a clinical trial. In the event that the Ethics Committee has any objections to the request for approval of a clinical trial or subsequent suggestions regarding proposed amendments or supplements to the conduct of a particular clinical trial, the Directive prescribes a single 60-day period for the Ethics Committee to submit comments to the applicant, to the sponsor of the trial, as well as to give a favourable or unfavourable opinion to the competent authority on the sponsor's request regarding the clinical trial.

8. In the preamble, the Directive refers only to 1996 version of the Helsinki Declaration. Since the Directive was adopted in 2001, the positions of the Declaration of Helsinki have been revised several times since its adoption. It is known from comparative medical and pharmaceutical law that some of the new standards are supported, and some are challenged from an ethical and scientific point of view.[8] Therefore, the possibility of adopting new regulations at the EU level should not be ruled out. Such regulations would include some new ethical and scientific standards created within the framework of the Helsinki Declaration. In any case, it can be concluded that in the legislation of the state of Serbia, this Directive has been implemented with its current text.

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