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BOOK REVIEW

MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ACCORDING TO THE DECLARATION OF HELSINKI

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1. The monograph under the above title discusses the Declaration of Helsinki (DoH) and its legal norms. In international public law, the DoH is a general international legal act containing medical, legal and ethical aspects of medical researches involving human subjects. The Constitution of the Republic of Serbia stipulates that there are two types of general international legal acts in the international community. Pursuant to Article 194, Paragraph 4 of the Constitution of the Republic of Serbia, these acts include ratified international treaties and generally recognised rules of international law. DoH is not an international treaty, a convention or a multilateral agreement of states, so it does not require confirmation and ratification in order to become part of the legal system of the Republic of Serbia. DoH belongs to generally recognised rules of international law because it contains generally accepted rules of international medical law. These generally accepted rules of international medical law have been appropriately incorporated into domestic legislation, and on that basis they became part of the legal system of the Republic of Serbia. In the international community, the DoH was developed in 1964 in Helsinki. It was amended several times since then, and the monograph covered seven amendments to the DoH up to and including 2013. International medical law rules were gradually incorporated into national legislations in the world, and the legislation of the Republic of Serbia. Generally accepted international rules of medical law in the monograph were presented with reference to the amendments to the DoH, but the focus was on medical researches involving human subjects.

2. This monograph is important for the insurance sector. A reader from the insurance sector, regardless of whether he/she is an employee or a member of the management board of an insurance or reinsurance company, can find an explanation for the rules of medical law and medical terminology in the monograph on the DoH. However, the rules of medical law and medical terminology are incorporated into the positive laws and bylaws of the Republic of Serbia, but some medical terms and some rules of medical law can be understood only with the use of appropriate medical dictionaries. In this monograph several medical and legal rules and unknown medical terms were explained in words that are clear to a layman. In that regard, it is worth consulting the register of terms at the end of the book, and the Serbian expression for a foreign word from the law – 'randomized' can serve as an example. There is a long list of positive laws in the Republic of Serbia, which incorporate international medical and legal rules and medical terminology originating from amendments to the DoH, with no published comments on laws from that list. Specifically, on the list of positive laws the first place is taken by international medical and legal rules and medical terminology on which the Law on Medicines and Medical Devices was conceived.[1] The law stipulates legal rules for various forms of medical researches involving human subjects and animals, including compulsory third party liability insurance for clinical trials of medicines, for example in the fields of medicine, pharmacy, psychiatry, dentistry, veterinary medicine, etc. Of course, sponsors and insurers may conclude various voluntary compulsory liability insurance with individual participants in a clinical trial under that law. Also, international medical and legal rules regarding medical researches are contained in the new law on medical devices.[2] The said law not only contains the rules of medical researches on medical devices, which were promoted by amendments to the DoH, but also stipulates at least one form of compulsory third party liability insurance for clinical trials of medical devices. In addition, the international medical and legal rules, contained in amendments to the DoH, best explain the solutions from the Law on Patients' Rights.[3] That law stipulates numerous medical and legal rules from the DoH, and also stipulates the obligation for the state health institution to conclude a compulsory liability insurance due to medical researches conducted on patients. Furthermore, the Health Protection Act[4] introduced novelties in the competence of ethics committees, both at the level of the state health institution and at the level of the Republic of Serbia, all in relation to the procedure of approval and control of clinical trials. This is important because the monograph pays special attention to the interpretation of international medical and legal rules from the DoH regarding the position and role of ethics committees.

[1] *Official Gazette of the RS,* no. 30/2010, 107/2012, 105/2017 – state law, 113/2017 – state law.
[2] *Official Gazette of the RS,* no. 105/2017.
[3] *Official Gazette of the RS,* no. 45/2013 and 25/2019 – state law.
[4] *Official Gazette of the RS,* no. 25/2019.

By no means should it be considered that the above list of positive laws completely exhausts the list of laws where an employee or a manager in the insurance sector can seek an explanation for certain rules of medical law and medical terms. These laws include the Transplantation of Human Organ Act,[5] the Law on Human Tissues and Cells,[6] the IVF Law,[7] the Law on Transfusion Medicine[8], etc. Therefore, the monograph can contribute to a better understanding and implementation of positive laws and bylaws in the Republic of Serbia in the insurance sector, since there are no published comments on key laws in the field of medical law.

3. The monograph consists of an **introduction**, four chapters, conclusion, literature and registry of terms. In the introduction, the authors presented two arguments leading to the development of international medical law in relation to medical research involving human subjects. The first argument started with the statement that there are numerous diseases for which there is no complete healing. Since medicine is applied science serving the preservation of people's health and treatment of diseases it requires new medical achievements. Authors of the monograph believed that this argument encouraged the development of medical research involving human subjects worldwide. In the second argument, authors pointed out that by participation of a human being in medical research, the necessary data for response in the research was provided. Hence, the second argument is rounded with a conclusion that a medical research aimed not to improve the health of a particular participant, but to develop general knowledge necessary to improve health of future patients. By participating in medical researches, participants did not exercise personal health benefit, but (highlighted in the monograph) exposed themselves to the risk that their lives or health was endangered, and they sacrificed themselves for the development of science and society. According to the reviewer of this monograph, the authors sent a message to readers that the development of medical research involving human subjects led to a possible conflict of interest in medical research involving human subjects.

4. The monograph started with the distinction between the position and the role of participants engaged in medical research involving human subjects. Authors first determined that amendments to the DoH did not define participants in medical research involving human subjects. However, authors deemed the term 'subject', which was used in literature and legislation, as more appropriate term in medical research involving human subjects. Hence the authors distinguished all subjects involved in medical research according to the criterion of the category to which that subject could belong. According to that criterion, sponsors and researchers would be in the

[5] *Official Gazette of the RS,* no. 57/2018.
[6] *Official Gazette of the RS,* no. 57/2018.
[7] *Official Gazette of the RS,* no. 40/2017 and 113/2017.
[8] *Official Gazette of the RS,* no. 40/2017 and 113/2017 – state law

first category. They explained that this category of subjects organizes and conducts medical research involving human subjects. They specified in the monograph that participants are in the second category of subjects. Participants are involved in medical researches. The monograph classified research ethics committees, inspection bodies and the competent ministry in the third category of subjects. Regarding the third category, they specified that the ethics committees approve and control a specific medical research, and the inspection bodies and the ministry supervise the ethics committees. It was stated that the rights and obligations of the first and the third category of subjects in medical research involving human subjects are aimed at protecting the rights and obligations of participants, and that the functions of the first and the third category of subjects are to balance the conflict of interest related to that medical research.

5. When presenting the international medical and legal rules from the amendments to the DoH, the authors used the following two basic concepts: health and patient. The definition of health by the World Health Organization from 2006 is used in the monograph. It reads: Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Definition of patient from the applicable Law on Patients' Rights was used in the monograph. This definition reads: Patient means a person, either sick or healthy who requires healthcare or to whom healthcare is provided for the purpose of preserving and improving health, prevention, control and early detection of diseases, injuries and other health disorders and timely and effective treatment and rehabilitation. As for other terms related to medical research involving human subjects, they have been identified in the monograph with regard to the topic being presented.

6. The title of the first chapter is **"Emergence and Development of International Regulations for Medical Research Involving Human Subjects."** Over 60 pages present the historical development of medical experiments on human subjects from ancient times to modern medical research involving human subjects. International medical law began to develop only in the middle of the 20th century. General international legal sources of medical law regarding medical research involving human subjects are listed, as well as national regulations of the states that preceded the adoption of key international legal acts on medical research involving human subjects. According to the monograph, the medical legislation on medical researches involving human subjects gained momentum in the international community after the Nuremberg Trials held following World War II by the Allied forces where German physicians were tried before an international court for conducting in vivo experiments on prisoners. In this manner, the Nuremberg Code was created in the international community, and the original DoH was developed in 1964. International non-governmental organization of physicians met several times after 1964, usually in world capitals, so that the original DoH was amended in 1975, 1983,

1989, 1996, 2000, 2008 and 2013. In the monograph, each of these amendments was considered separately, indicating which of them brought something new for medical researches involving human subjects.

7. Presenting the international medical and legal rules from amendments to the DoH, **the authors criticized seven amendments to the DoH for not systematizing participants in medical research involving human subjects.** Thus, the question of implementation of international medical law to medical research involving human subjects was open to discussion. Applying a functional approach to the role of each participant in medical research involving human subjects, the authors classified all participants of the research into three categories of subjects with more detail on this in point 4 of this review. Not only is this functional approach to subjects in medical research important from the point of view of implementation of international medical law, but it is also important from the point of view of insurance law. Namely, different categories of subjects in medical research involving human subjects appear in the insurance sector as insured persons, policyholders and insurance beneficiaries. In this regard, there may be various insurance contracts by subject matter, by duration, etc. It is specified in the monograph that the liability of a researcher towards a participant, and the liability of a sponsor, comprises of achieving a required quality consent for his/her participation in that medical research. Furthermore, it is highlighted that a researcher can only be a scientifically qualified person who possesses a high degree of knowledge and skills. In this regard, it was emphasized that a researcher should have appropriate expertise and medical experience in order to be able to assess at all stages of medical research whether further participation of subjects in that medical research would or could lead to a permanent damage to his/her health, injury or death. In this manner, the authors exhausted one aspect of implementation of the rules of international medical law to medical research involving human subjects. As for the next aspect important for implementation of the rules of international medical law to medical research involving human subjects, according to the monograph, it referred to the methods of compensating the damage that a participant would sustain during medical research. The authors pointed out that the amendment to the DoH from 2008 introduced novelties in that area. In the amendment to the DoH from 2008 (Section V, point 14) previous formulations were supplemented in favour of greater rights of participants to compensation for damage caused by medical research. Namely, several methods to compensate participants if they sustain any damage caused by medical research were anticipated. As one of methods to compensate the damage caused to a participant, the amendment to the DoH from 2008 stipulated insurance of participants during medical research involving human subjects. The amendment to the DoH from 2008 enabled the national legislator to introduce liability insurance in favour of participants - insurance beneficiaries for any damage to health, bodily injury or

death. Based on previously concluded third party liability insurance contract an insurer is obliged to compensate the damage to a participant, a third party instead of a sponsor, the insured. The monograph states that many national legislators even prescribed the introduction of compulsory liability insurance for damage caused to an insurance beneficiary - participant in connection with medical research. Therefore, rules of the DoH contributed to the development of third party liability insurance during medical research involving human subjects, and the merit of the monograph is that it pointed this out to a domestic reader.

8. The second chapter is entitled **"The Concept, Goal and Subject of Medical Research Involving Human Subjects."** For the insurance sector, this chapter of the monograph can be inspiring if an insurer previously decided to introduce a new insurance service related to medical law. In that case, an insurer must first prepare general or special insurance terms and conditions for certain forms of third party compulsory or voluntary liability insurance. In our conditions, it is, of course, about the implementation of some positive laws listed in point 2 of this review. When formulating these insurance terms and conditions, which will be an integral part of future insurance contracts, an insurance company is faced with a series of finesse in relation to the subject of regulations, which originate from medicine, psychiatry, dentistry, pharmacy, veterinary medicine, etc. This chapter of the monograph indicated, for example, the subject of biomedical research, which in our country can be the subject matter of general or special insurance terms and conditions. At the same time, the authors drew attention to the fact that, according to the World Health Organization, biomedical research is a broader concept than medical research involving human subjects. Biomedical research can have as its subject of research - medicines, medical devices, medical radiation, surgical procedure, medical imaging, biological sample, and it can also be research related to medical data, epidemiological topics, etc. Subject of biometric research pointed to diversity of subjects of biomedical research, which should be normatively expressed in insurance terms and conditions because of a long list of positive laws in the medical law in the Republic of Serbia. Therefore, for adequate formulation of general or special insurance terms and conditions in an insurance company, both for medical research involving human subjects and for biomedical research, encyclopaedic knowledge of medical and legal matter and a high degree of normative legal skill is required, if actuaries previously processed appropriate statistical data series and gave a positive evaluation for formation and emergence of a new insurance service on the market.

9. The second chapter of the monograph not only pointed out the subject of medical researches involving human subjects and the distinction from other related researches, but also enabled a closer understanding of the form of medical research involving human subjects. Interpreting the amendments to the DoH, the authors of the monograph stated that medical research involving human subjects

can be organized in two forms. One form would be experimental intervention characterized by a new or experimental intervention on human subjects, so that the effects on human subjects are observed, their safety and data on these effects are collected. In that form of medical research involving human subjects, researchers divide subjects in two or more groups where one or more groups of subjects receive a new intervention, while the other or several groups make a control group that does not receive the new intervention, and may be a placebo group (meaning without treatment). Another form of medical research involving human subjects is the observational medical research. In this form, no experiment is conducted, but the observed characteristics are recorded or collected data are analysed. Interpretation of amendments to the DoH enabled the authors to fully define the elements of the concept of medical research involving human subjects as follows: medical research involving human subjects is a systematic collection, description, analysis and interpretation of data related to implementation of preventive, diagnostic and therapeutic interventions. During these researches, human subjects are exposed to manipulation, intervention, observation or interaction with the researcher directly or indirectly. Previous presentation in this point shed more light on the concept of medical research involving human subjects, which can be reflected in the insurance sector. Before concluding an insurance contract an insurer should clearly distinguish with the insured the type of research and the subject of the research, and then develop general or special insurance terms and conditions. Thus, the presentation in the monograph indicated that medical law and insurance law can work closely and successfully when it comes to medical research involving human subjects.

10. The third chapter is the most extensive part of the monograph. It covers about 150 pages and discusses the rules from amendments to the DoH in relation to the **subjects of medical research involving human subjects**. It is divided in four sections, of which the first section dealt with participants, the second section dealt with researchers, and the third section dealt with sponsors of medical research involving human subjects. The fourth section focused on subjects approving, controlling and supervising the medical research involving human subjects. Each section is divided into subsections. The first section on participants included three subsections of about 100 pages, which is understandable if we bear in mind that this is the most sensitive part of medical research involving human subjects concerning both medical law and insurance law. Namely, the first subsection refers to the concept of subjects and character of their participation in research. The second subsection deals with general conditions for the participation of subjects in medical researches, while the third subsection sets out additional conditions for participation of vulnerable subjects in medical researches. In terms of the number of pages, the second section of the third chapter is shorter than the first section of the same chapter, but it is more diverse in structure than the first subsection in the sense that it has four subsections. The

subject of the first subsection are tasks and role of researchers in conducting medical research involving human subjects. The second subsection deals with the rights of participants who are subject of protection in the context of conducting medical research involving human subjects. The third subsection analyses competencies of researchers, while the fourth subsection examines researchers' liability for violating the protected rights of participants. The third section of the third chapter promotes sponsors of medical research and is the shortest in the third chapter in terms of volume with two subsections. The first subsection discusses provision of access to experimental intervention upon completion of a clinical trial, and the second subsection deals with the sponsor's obligations regarding the publication of research results. The fourth section of the third chapter deals with research ethics committees, more precisely their competencies, composition and organization, independence and liability for medical research involving human subjects.

11. The title of the first section in the third chapter is **'Participants'**. According to the monograph, a participant can be defined in two ways, depending on the form of medical research involving human subjects. The first way implies that a participant is a natural person whose human material, data or reactions of the body during the experimental intervention can give a relevant answer to the question from the examination. This definition in the monograph covers a participant in experimental medical research involving human subjects. The medical term - human material - includes human tissues, organs, blood, plasma, skin, serums, DNA, RNA, proteins, cells, hair, nails, urine, saliva and other body fluids. Another way of defining a participant envisages that a participant is a natural person who is the subject of observation in order to collect and analyse data required to solve the problem defined in the research. In the latter method of defining participants, the monograph defined a participant in the medical observational research. In medical experimental research, participants are persons who are assigned to the group that receives the experimental intervention, then persons who receive another effective intervention, and finally persons who receive a placebo. In any case, it was concluded in the monograph that participants differ from other participants in medical research since only they bear the risks, burdens and consequences associated with conducting the experiment and only their rights and their subjectivity through the experiment can be violated by acquiring general knowledge relevant to science and society. It is stressed in the monograph that rules of the DoH stipulate three general conditions for the consent of a natural person to become a participant in medical research involving human subjects. The first condition envisages that a natural person is capable of giving consent, and if he/she is not able to do so, the consent should be given by his legal representative. The second condition is that the future participant is informed of all relevant facts for his/her participation in the research and that he/she understood those facts. The third general condition envisages that the consent

is not given under duress and that it is desirable that the consent be signed and in writing. Preparation of general conditions for participation of subjects in medical research included a number of questions in the monograph. Among them are the consent of participants and quality of the consent of participants, then the ability to consent and that participants have all information before giving consent, as well as the voluntariness of giving consent and the statement of consent of participants. In addition to general conditions for participation of subjects in medical research, the monograph also discusses additional conditions for participation of subjects - vulnerable persons in medical researches. First of all, the monograph states that the DoH did not define vulnerable persons, so the Guidelines for Good Clinical Practice were used, translated into Serbian and published in the Official Gazette of the RS. The monograph cited the term 'vulnerable persons' from these guidelines, but their protection is, of course, considered with regard to several amendments to the DoH. From the point of view of insurance law, non-implementation of protection of participants, and especially vulnerable participants, is the most important series of problems in practice. Sponsor selects the researcher, and as an insured person concludes a liability insurance contract with an insurer, which protects a participant as an insurance beneficiary - a third party - in advance from any mistakes made by a researcher or any of persons subordinate to the principal researcher in that research. It is in the interest of sponsors and researchers to try to finish the research, so in comparative insurance practice mistakes happen in previously described protection of participants, especially vulnerable people. Mistakes and other omissions towards participants during medical research result in damage to their health, bodily injury or even death, so the sponsor is liable for any damages if he has not previously concluded a liability insurance. If the sponsor concluded the third party liability insurance and a participant sustained any damage, the participant's claim is filed against the insurer. Insurers in Europe, and also in our country, based on concluded liability insurance contract for any damages caused to a participant due to participation in medical research involving human subjects, usually pay a significant amount of compensation, satisfying the claims of participants in order to avoid reputational risk. Therefore, an insurance company has a great interest to get acquainted with the international medical and legal rules from the DoH and to incorporate them into the insurance policy for medical research involving human subjects, and for that the company charges significant amounts of insurance premium from the sponsor of medical research.

12. The second section in the third chapter deals with **researchers**. The authors pointed out that the DoH referred to researchers as physicians, and the authors believe that they should be called researchers. Argument for this is that physicians in medical research involving human subjects are treated both as physicians and as scientists. Authors of the monograph believe that each researcher should have

at least a specialization in the field that is the subject of medical research involving human subjects, as well as that it is necessary for researchers to adhere to the protocol established for that research. Since the DoH did not explore researchers' responsibility, the monograph assessed that the DoH left the issue to national regulations. This indication in the monograph may mean to a reader an invitation to create services in the domain of voluntary insurance of researchers, physicians, veterinarians and pharmacists in medical research involving human subjects. In insurance practice in Europe, and also in our country, usually sponsors as insureds can conclude a liability insurance contract with insurers for any damage caused to a researcher or a research team member in a specific medical research involving human subjects, but a researcher can conclude an insurance contract against own liability for participation in medical research.

13. The fourth section in the third chapter of the monograph is dedicated to **subjects that approve, control and supervise conducting of medical research involving human subjects**. The monograph specified that many interests are acquired in the work of a research ethics committee. It is stated that the interest of the sponsor of medical research involving human subjects is to start the research, conduct it without delays and problems, hire competent researchers and get a positive outcome, as well as justify the invested funds, all of which would enable the sponsor to later multiply profits. It is also emphasized that the researcher's interest is to participate in valid innovative medical research, to complete a research efficiently and thus gain points for further career success, as well as to receive adequate financial compensation for the work. Finally, it was highlighted that there was an interest of participants who hoped that by participating in a medical research they would help themselves by providing a state of health devoid of previous ailments, pain and illness. It was stated in the monograph that potential conflict of the stated interests are important issues of research ethics committees such as their competence, organization and composition, as well as their independence and responsibility in their work.

14. The basic ethical principles of conducting medical research involving human subjects are the topic of the fourth chapter of this monograph. The emphasis is on several ethical principles important for conducting medical research involving human subjects. Authors of the monograph reformulated the principle of protection of participants' interests from the DoH into the principle of respecting the rights and dignity of participants. Furthermore, they pointed out that the principle of scientific basis of medical research can be derived and formulated from the DoH, then the principle of necessary independent assessment of research protocol, then the principle of evaluating the relation between risks and benefits from research, and finally the principle of informed consent by a participant. Each of the stated principles was considered and comprehensively evaluated.

15. Conclusion of the monograph pointed out that after seven amendments the DoH there is still room for improvements in protection of participants in medical research involving human subjects. It was emphasized that the DoH has evolved in the direction of general and additional protection measures for every group of participants in medical research. Evolution of the DoH is critically observed in the sense that there is still no definition of vulnerable participants in medical research. In addition, the conclusion highlighted that the use, engagement of persons participating in medical research who do not possess a legally relevant will as a means of improving science and society is in fact an abuse of those persons. Authors of the monograph advocated further amendment of the DoH and additional protection of persons who are physically or mentally incapable of giving consent to participate in a research, and who remained unconscious. During medical research involving human subjects, researchers-physicians do not treat patients, but act as scientists so they can take actions contrary to the best interests of patients. Reconciliation of these two roles of physicians was resolved by the evolution of the DoH in a satisfactory manner, that is, by the medical and legal rule that the development of medicine in research has no advantage over the interest of any participant in that research. In conclusion, it is noted that the DoH did not regulate in detail the rights and obligations of medical research sponsors. A remark was made in the monograph regarding the idea of research ethics committees in the DoH. Namely, the DoH anticipated the right of ethics committees to pre-approve a specific research and then control the protocol and the research itself, but did not formulate the obligation of ethics committees to check fulfilment of conditions under which the research was approved and conducted. Compared to the basic principles for conducting medical researches, the monograph concluded the following: medical research involving human subjects can be validly and scientifically explained in the beginning, but on the scale of social significance that research may have little or no social significance, so it is recommended that the DoH will in future make a step in that direction.

16. After the conclusion, at the end of the book, extensive **literature** and a good **register of terms** were printed. In that manner, one scientifically valuable work in the field of medical law was completed, which is also important from the point of view of medical insurance law. Since the monograph is written in a clear style using scientific instruments and the **Cyrillic alphabet**, it has both scientific and practical value for a wide range of readers. Namely, the potential circle of readers of this monograph should be sought in the healthcare, state administration and self-government (at the level of the RS, provinces, cities and municipalities), in clinical centres and their ethics committees, including the ethics committee formed at the level of the Republic of Serbia, as well as at faculties of medicine, faculties of dentistry, pharmaceutical, veterinary, law and other faculties in the country and abroad where active programs, specialist and doctoral courses and courses in medical,

pharmaceutical and related branches of law are active. In the Republic of Serbia there is a long list of positive laws and bylaws in the medical and pharmaceutical law. In this review, the monograph is recommended to employees and managers (in executive and supervisory boards) in insurance and reinsurance companies, including the insurance sector in the National Bank of Serbia, given that a long list of positive laws is described in more detail in this review.

Translated by: ***Jelena Rajković***