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Biomedical Research on Vulnerable Subjects in Bosnia and Herzegovina

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Abstract: Medical research involving human subjects can enhance the well-being of individual patients and provide enormous social benefits. It enables the acquisition of new scientific knowledge and the development of novel therapeutic and diagnostic procedures but also raises significant ethical and legal issues. This kind of medical research is controversial and implies a clash of values that are not always easy to balance. Particularly contentious is research on subjects who are incapable of giving consent or are in a position of subordination and more susceptible to manipulation and mistreatment. Such subjects are considered vulnerable and under special protection. The paper deals with the legal framework of medical research on vulnerable subjects in Bosnia and Herzegovina (its entities: the Republic of Srpska and the Federation of Bosnia and Herzegovina). In the first part of the paper, the notion and basic forms of medical research will be explored, as well as the concept of vulnerability. Reference will be made to relevant international documents defining the standards of medical research on vulnerable subjects. The paper will also provide a comparative overview of provisions governing vulnerable subjects research adopted in different national legislations. In the second part of the paper, the legal framework of medical research on vulnerable subjects in Bosnia and Herzegovina will be analyzed, and suggestions for possible changes will be made.

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1. Introduction: On Relevance and Controversial Nature of Biomedical Research on Human Subjects

The term biomedical research refers to "all types of clinical investigations that have as their ultimate aim the pursuit of clinical knowledge, including those that have a partial therapeutic intent and those that do not."[1] Medical research differs from medical practice in several important ways. Medical practice typically follows established clinical guidelines and protocols based on evidence from prior research and clinical experience. It includes standard treatments that doctors of the same speciality commonly apply. If a new procedure (or medication) is used instead, which has not been previously recognized or applied by many physicians, it represents medical research.[2] Knoppers and Sprumont identify three main differences between medical practice and research. First, while the primary goal of medical practice is to enhance the health and/or well-being of an individual patient, the researcher's goals include those of the medical research itself (the researcher does not act exclusively in the interest of a research subject). Second, the doctor-patient relationship is highly personal, and all physician's activities should be based exclusively on the specific needs of the patient. On the other hand, a researcher must strictly follow the procedures stipulated in the research protocol. Third, research should be based, in principle, on a written protocol defining its purpose, goals, and means, which is "necessary not only to guarantee the quality and reliability of the research results but also to protect the human subjects against unnecessary and unpredicted risks and burdens."[3]

Two basic types of medical research are therapeutic and non-therapeutic. Therapeutic research can be broadly defined as "research that offers some therapeutic benefit to the person participating in the study."[4] Participants in this kind of research "are patients expecting to be treated for their illness as well as to help the researcher gain knowledge which

1 Philip Bielby, *Competence and Vulnerability in Biomedical Research* (Springer, 2008), 50.

2 Jakov Radisic, *Medicinsko pravo* (*Medical Law*) (Beograd: Nomos, 2008), 255.

3 Bartha Maria Knoppers and Dominique Sprumont, "Human Subjects Research, Ethics, and International Codes on Genetic Research," in *Encyclopedia of Ethical, Legal and Policy Issues in Biotechnology*, eds. Thomas H. Murray and Maxwell J. Mehlman (New York: John Wiley and Sons, 2000), 2: 568.

4 Leanne Bell, *Medical Law and Ethics* (Harlow: Pearson Education, 2012), 239.

can be generalized."[5] On the other hand, non-therapeutic research encompasses studies that do not directly aim to benefit individual subjects. Participants in non-therapeutic research are not expected to gain any therapeutic benefits from their involvement. Its primary objective is to generate knowledge, advance scientific understanding, or develop theories. Some authors claim that since research and therapy are fundamentally different, speaking of "therapeutic research" is contradictory, and the term should be abandoned.[6] The term therapeutic research is criticized as ambiguous because it implies some therapeutic benefits for participants, even though these benefits are only hypothetical. It also creates confusion about the exact role of physicians involved in the research process (who, in the context of research, act primarily as investigators, not healers).[7] Bell also complains that the term "non-therapeutic" research is misleading as it suggests that this type of research is somehow of less value; while it may have considerable benefits for persons other than those participating in the study, perhaps sometime after the research is carried out.[8] Levine, who opposes the aforementioned distinction, points out that "[t]he class of activities covered by the term 'therapeutic research' is also problematic because all clinical trials of therapeutic agents include some components that may be therapeutic (...) and others that are clearly nontherapeutic."[9] Those who rely on the distinction between therapeutic and non-therapeutic research will usually categorize research protocols with one or more therapeutic components as therapeutic research. As a consequence, all components of such protocols will be evaluated/justified according to relatively permissive standards for therapeutic research (Levine calls this phenomenon the "fallacy of the package deal").[10] Although the distinction between therapeutic and non-therapeutic research has been abolished in some national

5 Claire Foster, *The Ethics of Medical Research on Humans* (Cambridge: Cambridge University Press, 2004), 38.

6 Knoppers and Sprumont, "Human Subjects Research, Ethics, and International Codes on Genetic Research," 568.

7 Ibid.

8 Bell, *Medical Law and Ethics*, 239.

9 Robert J. Levine, "The Need to Revise the Declaration of Helsinki," *The New England Journal of Medicine* 341, no. 7 (1999): 531.

10 Ibid.

legislations (in the United States (US) and Canada as far back as the 1970s)[11] and relevant international documents (the Declaration of Helsinki),[12] it still significantly impacts the regulatory framework of medical research in the majority of European countries.[13]

Medical research on human subjects is of utmost importance. It can enhance the well-being of individual patients and provide enormous social benefits. It is indispensable for advancing medical knowledge, improving healthcare outcomes, and addressing public health issues. Medical progress depends on medical research, which, ultimately, requires the involvement of human subjects.[14] As certain authors point out: "One thing is undisputed in the very controversial field of clinical trials: medical research is absolutely necessary."[15]

However, it also raises numerous ethical and legal dilemmas. Medical research involving human subjects is necessarily controversial and implies a confrontation of values that are not always easy to balance. As Jay Katz notes: "When science takes man as its subjects, tensions arise between two values basic to Western society: freedom of scientific inquiry and protection of individual inviolability."[16] Medical research on human subjects touches upon their right to life and physical integrity. Although medical treatments also put patients at risk, "the risks involved in the biomedical research tend to be graver, since the methods used have not yet been proved, and their effects may not all be known."[17] This kind of medical research is also problematic from the perspective of protecting the value of human dignity. A certain degree of instrumentalization, necessarily present in medical

11 Ibid.

12 The distinction between "therapeutic" and "non-therapeutic" research was abolished in the 2000 revision of the Declaration (Karmela Krleza-Jeric and Trudo Lemmens, "7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials," *Croatian Medical Journal* 50, no. 2 (2009): 106).

13 Radisic, *Medicinsko pravo* (*Medical Law*), 256.

14 Henning Rosenau, "Legal Prerequisites for Clinical Trials under the Revised Declaration of Helsinki and the European Convention on Human Rights and Biomedicine," *European Journal of Health Law* 7, no. 2 (2000): 105.

15 Ibid.

16 Jay Katz, *Experimentation with Human Beings* (New York: Russel Sage Foundation, 1972), 1, quoted in Knoppers and Sprumont, "Human Subjects Research, Ethics, and International Codes on Genetic Research," 567.

17 Rosenau, "Legal Prerequisites for Clinical Trials," 106.

trials, makes research on human subjects morally problematic (because it can potentially cause the violation of the second formulation of Kant's categorical imperative: never treat a person merely as a means to someone else's end but always also as an end in themselves). The protection of the dignity of an individual requires that participation in medical research be based on the subject's voluntary informed consent (as the principle deeply entrenched in the concept of "dignity as empowerment").[18] However, the problem of informed consent, or respect for individual autonomy/dignity, is not the only issue relevant from the perspective of human dignity protection. The subject's consent may not always be sufficient to legitimize medical research. The other Janus face of human dignity ("dignity as constraint") also comes to the fore in the context of human subject research. Controversial issues in which the constraining dimension of human dignity plays a role, as some authors note, are the experimentation on human embryos or the mixing of human and non-human DNA[19] (but also other research that is potentially problematic from the perspective of respect for public morality). The importance of human dignity protection, in both its empowering and constraining sense, has been explicitly highlighted in some national research ethics guidelines. For example, Canada's *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* from 1998 provided for the obligation to respect inherent dignity as a moral absolute (one should never treat others merely as a means to an end) but also stressed the fact that all of humanity can be impoverished by research that shows disrespect for human dignity.[20]

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18 Beyleveld and Brownsword differentiate between "dignity as empowerment" and "dignity as constraint". According to the authors, the conception of "dignity as empowerment" implies that "the function of human dignity is to reinforce claims to self-determination rather than to limit free choice" (Deryck Beyleveld and Roger Brownsword, *Human Dignity in Bioethics and Biolaw* (Oxford: Oxford University Press, 2001), 28). On the other hand, the conception of "dignity as constraint" acts as "a constraint on free choice" (Ibid., 11).

19 While many researchers and consumers argue that respect for their inherent dignity justifies granting a free hand in research on human subjects, others oppose and call for greater regulation on the grounds of protecting dignity (Lawrence Burns, "What is the Scope for the Interpretation of Dignity in Research Involving Human Subjects?," *Medicine, Health Care and Philosophy* 11, no. 2 (2008): 193–4).

20 Ibid., 191.

Thus, the remark made by Jean Bernard, the first chairman of the French National Ethics Committee, about human experimentation as "morally necessary and necessarily immoral" is not without merit.[21] Particularly controversial is research performed on subjects who are unable to give consent or are in a position of subordination and more susceptible to pressure and manipulation. Such subjects are considered vulnerable and under special protection (which will be explored in more detail within this paper).

2. The Concept of Vulnerability in Medical Research on Human Subjects

Medical research on vulnerable subjects refers to studies that involve individuals or groups who are "presumed to be more likely than others to be misled, mistreated, or otherwise taken advantage of as participants in research."[22] A vulnerability status generates an obligation for legislators, researchers, and ethics committees to provide special protection for this category of subjects.

The term "vulnerable" originates from the Latin verb *vulnerare*: to wound. This original meaning of the term is still present today. The *Oxford English Dictionary*, for example, lists "susceptible of receiving wounds or physical injury" as a primary definition of "vulnerability".[23] However, the meaning of this term transcends mere susceptibility to physical harm. It also includes "a predisposition to certain types of psychological and/or developmental harm that an individual has an interest in avoiding."[24] Bielby differentiates between two meanings of vulnerability: (1) baseline vulnerability (which expresses the condition of all human beings as able to be hurt, wounded, or killed), and (2) heightened vulnerability (which relates to those individuals who are more susceptible than usual to being hurt or

21 Quoted in Knoppers and Sprumont, "Human Subjects Research, Ethics, and International Codes on Genetic Research," 567.

22 Carol Levine at al., "The Limitations of 'Vulnerability' as a Protection for Human Research Participants," *The American Journal of Bioethics* 4, no. 3 (2004): 44.

23 *Oxford English Dictionary*, 2nd ed., quoted in Bielby, *Competence and Vulnerability in Biomedical Research*, 52.

24 Bielby, *Competence and Vulnerability in Biomedical Research*, 52.

injured).[25] A heightened state of vulnerability can be caused by various cognitive and circumstantial factors, such as immaturity, old age, physical illness or injury, mental illness or impairment, socio-economic disadvantages, physical or psychological trauma, institutionalization, membership of a minority group that experiences prejudice or mistreatment, etc.[26] Depending on the factors that cause the individuals' heightened vulnerability, Bielby distinguishes between cognitive and circumstantial vulnerability (although, as the author points out, these two forms of increased vulnerability may overlap).[27] Both of these forms of heightened vulnerability are relevant in the context of human subject research.

The concept of vulnerability has long played a central role in discussions on research ethics.[28] One of the reasons for the frequent use of this term was a significant number of ethically problematic research recorded in medical practice.[29] However, the concept remains elusive despite the frequency with which the term vulnerability is used. Certain assistance in determining the meaning of this term can be provided by international documents and national regulatory acts governing research on human subjects. For example, the US Common Rule, the centrepiece of human research

25 Ibid., 53.

26 Ibid., 54. As stated in the CIOMS's "International Ethical Guidelines for Health-related Research Involving Humans", persons may be vulnerable when they have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests. However, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests (Commentary on Guideline 15) (Council for International Organizations of Medical Sciences (CIOMS), "International Ethical Guidelines for Health-related Research Involving Humans" (2016)).

27 Ibid. Individuals with mental disorders or intellectual disabilities and children are primarily cognitively vulnerable, while the economically disadvantaged, prisoners, the uneducated and persecuted are primarily circumstantially vulnerable (since the circumstances that make them vulnerable are contingent on social, political, and legal arrangements).

28 Carl H. Coleman, "Vulnerability as a Regulatory Category in Human Subjects Research," *The Journal of Law, Medicine & Ethics* 37, no. 1 (2009): 12.

29 Levine et al., "The limitations of 'vulnerability,'" 45; Michael G. White, "Why Human Subjects Research Protection is Important," *Ochsner Journal* 20, no. 1 (2020); Todd W. Rice, "The Historical, Ethical, and Legal Background of Human-Subjects Research," *Respiratory Care* 53, no. 10 (2008): 1327.

subject protection in this country, uses the term "vulnerable" three times.[30] Although the Common Rule does not define vulnerability,

> each time the word is used, it is accompanied by the phrase 'such as children, prisoners, pregnant women, or handicapped or mentally disabled persons' and, in two of the three sections, 'economically or educationally disadvantaged persons'.[31]

It is evident that the document refers to both forms of heightened vulnerability (according to Bielby's classification mentioned above). Some other relevant provisions related to vulnerability in research will be discussed below.

3. International and European Standards on Medical Research Involving Human Subjects

The Nuremberg Code[32] of 1947 provided the first international rules for scientific experiments on human participants. Introduced as a response to horrifying Nazi "medical" experiments, the Code "firmly established the principle of patient self-determination."[33] The opening line of the first of its ten principles states: "The voluntary consent of the human subject is absolutely essential." The Code's first principle also explicitly excludes vulnerable groups from medical experimentation. Medical experiments on persons who do not have legal capacity or are not able "to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion" are prohibited. The prohibition of medical experimentation on vulnerable subjects is also prescribed by the UN's International Covenant on Civil and Political Rights[34] (ICCPR) of 1966. Article 7 of the ICCPR excludes the possibility of

30 Coleman, "Vulnerability as a Regulatory Category in Human Subjects Research," 12.

31 Ibid.

32 Nuremberg Code of 1947, *British Medical Journal* 313, no. 7070 (1996): 1448.

33 Jose Miola, *Medical Ethics and Medical Law. A Symbiotic Relationship* (Oxford: Hart Publishing, 2007), 34.

34 The International Covenant on Civil and Political Rights, United Nations (1966), accessed February 28, 2024, https://www.ohchr.org/en/instruments-mechanisms/instruments/international-covenant-civil-and-political-rights.

medical experimentation without a subject's free consent.[35] The exclusion of vulnerable persons or groups from medical research due to rigid voluntary consent requirements has been criticized since it deprives some individuals of the right to participate in clinical trials.[36] The General Medical Council's 2002 guidance "Research: The Role and Responsibilities of Doctors" suggests that excluding vulnerable research subjects could be considered a form of discrimination.[37]

The Declaration of Helsinki (DoH),[38] adopted by the World Medical Association (WMA) in 1964 (amended seven times since, the latest revision made in 2013), is described in the literature as "the first attempt to formulate a universal code for the practice of medical research"[39] and "the cornerstone document of human research ethics."[40] The Declaration describes vulnerable groups and individuals as those who "may have an increased likelihood of being wronged or of incurring additional harm" (Article 19). Unlike the Nuremberg Code and the ICCPR, the Declaration allows medical research on vulnerable subjects under certain conditions. According to Article 20 of the Declaration, medical research with vulnerable groups is only justified if it is responsive to the group's health needs or priorities and the research cannot be carried out in a non-vulnerable group. This article also requires that a vulnerable group should stand to benefit from knowledge, practices, or interventions that result from research. If a potential research subject is incapable of giving informed consent, the physician must seek informed consent from their legally authorized representative

35 Ulf Schmidt, "From Nuremberg to Helsinki: Historicizing the Codification of the Post-War Research Ethics," in *Ethical Innovation for Global Health: Pandemic, Democracy and Ethics in Research*, eds. Chieko Kurihara, Dirceu Greco, and Ames Dhai (Springer, 2023), 154.

36 Mary C. Ruof, "Vulnerability, Vulnerable Populations and Policy," *Kennedy Institute of Ethics Journal* 14, no. 4 (2004): 411.

37 General Medical Council, "Research: The Role and Responsibilities of Doctors," 2002, para. 43, quoted in Bielby, *Competence and Vulnerability in Biomedical Research*, 51.

38 World Medical Association, The Declaration of Helsinki, 1964 (the 2013 version), accessed February 27, 2024, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

39 Stuart J. Horner, "Retreat from Nuremberg: Can We Prevent Unethical Medical Research?," *Public Health* 113, no. 5 (1999): 205.

40 Badri Shrestha and Louese Dunn, "The Declaration of Helsinki on Medical Research involving Human Subjects: A Review of Seventh Revision," *Journal of Nepal Health Research Council* 17, no. 4 (2019): 548.

(Article 28). Furthermore, the Declaration requires that minors or legally incompetent subjects provide their consent, indicating a strong commitment to respecting a research subject's person (i.e. their dignity). According to Article 29 of the DoH, when a potential research subject incapable of giving informed consent can give assent regarding their participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative (the potential subject's dissent should also be respected) (Article 29).

In Europe, medical research on human subjects is regulated by the European Union (EU) law and the documents adopted by the Council of Europe (CoE). In the EU, the oversight of research with human participants is divided between EU-level law and the laws of the Member States.[41] Clinical medical research is subject to the Clinical Trials Regulation 536/2014[42] (which repealed the Clinical Trials Directive 2001/20/EC on 31 January 2022). Article 10 of the Regulation provides for specific considerations for vulnerable persons. Article 10(1) stipulates that:

> Where the subjects are minors, special consideration shall be given to the assessment of the application for authorization of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics.

The Regulation also considers incapacitated subjects and pregnant or breastfeeding women as a vulnerable population that requires special considerations (Article 10(2) and (3)). Research in the EU is also subject to a variety of human rights principles (some of which are derived from the EU's Charter of Fundamental Rights and are enforced by the European Court of Justice, but since the EU Member States are also members of the CoE, medical research in EU countries is subject to the jurisdiction of the European Court of Human Rights).[43]

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41 Carl H. Coleman, "Introduction to Research with Human Participants," in *The Oxford Handbook of Comparative Health Law*, eds. David Orentlicher and Tamara K. Hervey (New York: Oxford University Press, 2022), 609.

42 EU Clinical Trial Regulation no. 536/2014, accessed February 18, 2024, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0536.

43 Coleman, "Introduction to Research with Human Participants," 609.

In 1997, the Parliamentary Assembly of the Council of Europe adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine, also known as the Oviedo Convention),[44] considered as "one of the most important bioethics texts from the point of view of international policy and law."[45] Chapter V of the Convention (Articles 15–18) lays down general rules for biomedical research on human subjects. Article 15 of the Convention stipulates that research in the field of biology and medicine may be carried out freely but always subject to the provisions of the Convention and other legal provisions ensuring the protection of human beings. Article 16 determines the conditions for research on human subjects: no alternative of comparable effectiveness exists (e.g. animal research); the risks for the research subjects should not be disproportionate to the potential benefits of the research; the research project should be approved by the competent body after independent examination of its scientific merit; research subjects should give their free, explicit, and informed consent, in accordance with Article 5 of the Convention, which may be freely withdrawn at any time. Article 17 regulates research on persons not able to consent. This kind of research may only be undertaken if its results have the potential to produce real and direct benefits to a subject of research, and the research of comparable effectiveness cannot be carried out on persons capable of giving consent (the Convention also requires that the necessary authorization of a legally authorized representative be given specifically and in the written form). Exceptionally, research without direct therapeutic benefit may be authorized if it "entails only minimal risk and minimal burden for the individual concerned" (Article 17(2)).

In 2005, the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research[46] (Additional Protocol)

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44 The Parliamentary Assembly of the CoE, The Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, 1997, accessed February 26, 2024, https://rm.coe.int/168007cf98.

45 Gilbert Hottois, "A Philosophical and Critical Analysis of the European Convention of Bioethics," *Journal of Medicine and Philosophy* 25, no. 2 (2000): 133.

46 The Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (ETS no. 168), CoE, 2005, accessed February 24, 2024, https://rm.coe.int/168007f2ca.

was adopted. According to Article 3 of the Additional Protocol: "The interests and welfare of the human being participating in research shall prevail over the sole interest of society or science." Article 14(1) stipulates that no research on a person may be carried out without their "informed, free, express, specific and documented consent". Article 15 of the Additional Protocol regulates the protection of persons not able to consent to research. It stipulates that research on a person without the capacity to consent may be carried out only if the research results have the potential to produce real and direct benefits to their health, and research of comparable effectiveness cannot be performed on individuals capable of giving consent. The Additional Protocol requires that the necessary authorization be given specifically and in written form by the legal representative or an authority, person, or body provided for by the law. According to Article 15(1)(iv), an adult subject who is not able to consent should, as far as possible, take part in the authorization procedure. The Protocol also requires that the opinion of a minor should be taken into account "as an increasingly determining factor in proportion to age and degree of maturity" (Article 15(1)(iv)).

The Explanatory Report to the Additional Protocol, adopted by the Council of Europe in 2005, "contains the most detailed taxonomy of vulnerability in a contemporary ethical code."[47] The Explanatory Report provides an extensive classification of vulnerable groups according to cognitive, situational, institutional, deferential, medical, economic, and social factors (as pointed out in the Report, membership of these groups can overlap).[48]

Bosnia and Herzegovina ratified the Oviedo Convention and the Additional Protocol in 2007 (they came into force on 1 September 2007).

4. Comparative Overview of the Human Subject Research Regulation

For a long time, most countries have not had any ethical regulations for medical research. However, in many Western countries, the ethical framework regulating medical research on human subjects has been consolidated

47 Bielby, *Competence and Vulnerability in Biomedical Research*, 60.

48 The Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research, Council of Europe, 2005, accessed February 21, 2024, https://rm.coe.int/16800d3810.

since the 1980s.[49] The Federal Policy for the Protection of Human Subjects (the "Common Rule") came into force in the US in 1981. France adopted special legislation in 1988, establishing forty-eight Committees for the Protection of Persons throughout the country. Although the first research committees in Germany were established in the 1970s, committee approval of clinical trials was not mandatory until 1994.[50]

The current French Law no. 2012–300 of 5 March 2012 on research involving human subjects, known as "Jardé law", came into force in 2016. It stipulates that for adults who are protected or incapable of consenting (e.g. coma, senile dementia, psychiatric reasons, or enfeebled patients), authorization is required from the tutor or the curator for protected adults and minors (Article L.1122–2 II, §3), or from the designated person of trust, a family member by default, or a person with strong and reliable ties to the patient (as a last resort) (Article L.1122–2 PHC). When it comes to medical research on minors, in principle, both parents must consent to any interventional research on their child, whether it entails minimal risk or not (research categories 1 and 2) (Article L.1122–2 II PHC). Exceptionally, the present parent can give consent if the research involves minimal risks and two conditions are met: (1) the minor must not qualify as a healthy volunteer, and (2) the collection of the other parent's consent is incompatible in terms of time frame with the methodological requirements of the study with regards to its objectives (Article L.1122–2 II PHC). The Law differentiates between three categories of research involving human subjects: Category 1: interventional research implying an intervention that is not risk-free for the research subjects and is not justified by their usual care; Category 2: interventional research with minimal risks and constraints; Category 3: non-interventional research implying acts and procedures that are risk-free. The Law also stipulates that people deprived of their freedom by legal or administrative decisions or people benefiting from psychiatric care unable to express their consent can only participate in interventional research (categories 1 and 2) if the direct expected advantage for these subjects justifies the foreseeable risks or there is an expected advantage for

49 David F. Kelly, Gerald Magill and Henk ten Have, *Contemporary Catholic Health Care Ethics* (Georgetown University Press, 2013), 263.

50 Ibid.

people in the same situation, while the research cannot be conducted on other types of subjects (the Law, therefore, also regulates certain forms of circumstantial vulnerability).[51]

In Germany, participation in medical research of subjects incapable of giving consent requires the approval of their legal representatives. A potential subject's assent for participation in research is also needed, provided that the person is capable of understanding the nature, significance, and implications of clinical investigation and is able to form a rational opinion based on these facts. In clinical studies with minors, consent should be given by the legal representative. If the minor is able to understand the nature, significance, and implications of the clinical research, their assent is also required.[52] In Poland, a legally incapacitated person is required to provide written assent if they are able to consciously express their opinion. In cases of clinical research on minors, those over the age of 16 need to give their written assent (minors under 16 can also give their assent if they are able to express their own opinion).[53] On the other hand, Russian legislation does not provide for the inclusion of incapacitated persons or minors in the process of obtaining informed consent.[54] The Patients' Rights Act of Montenegro[55] also does not contain an assent requirement. It stipulates that scientific examination and research can be undertaken exceptionally on a minor or a patient deprived of legal capacity, but only for their immediate benefit and with the written consent of their legal representative, who has been previously informed about the purpose, goal, course of the procedure, expected results, potential risks, as well as possible side effects of testing and research (Article 23).

51 Elisabet Toulouse et al., "French Legal Approach to Clinical Research," *Anaesthesia Critical Care & Pain Medicine* 37, no. 6 (2018).

52 Marcin Orzechowski et al., "Normative framework of informed consent in clinical research in Germany, Poland, and Russia," *BMC Medical Ethics* 22, no. 1 (2021), accessed February 27, 2024, https://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-021-00622-6.

53 Ibid.

54 Ibid.

55 The Patients' Rights Act of Montenegro, Official Gazette of Montenegro, no. 40/2010 and 40/2011.

5. Legal Framework of Research on Vulnerable Subjects in Bosnia and Herzegovina

Bosnia and Herzegovina is a complex state community which consists of two entities: the Republic of Srpska (RS) and the Federation of Bosnia and Herzegovina (FBiH) (the Brcko District (BD) is a third territorial unit; BD is a small subnational unit that enjoys broad legislative autonomy). The distribution of competences between BiH and the entities is determined by the Constitution of BiH in such a way that BiH is assigned the competences for regulating issues that are expressly stated in the Constitution of BiH, while all other issues are solely the responsibility of the entities.[56] The BiH entities and the BD are responsible for regulating health protection in BiH.

In the RS, under Article 14(3) of the RS Constitution,[57] no person can be subject to medical or other scientific experiments without their consent. In accordance with the aforementioned constitutional provision, the RS Health Protection Law[58] (RS HPL) stipulates that medical research on an adult and legally competent patient can be conducted only with their informed consent given in written form. The RS HLP also regulates the participation in clinical research of persons incapable of giving consent. Under Article 52(2) of the RS HPL, clinical research on a minor or a person deprived of legal capacity may only be conducted in exceptional cases if there is an indication for medical treatment and when written consent is given by the minor's parent or guardian, or the legal representative of the person deprived of legal capacity.

The Code of Medical Ethics and Deontology of the RS Medical Doctor's Chamber[59] also regulates physicians' responsibilities related to medical research. Article VI(3) of the Code states that physicians must adhere to the Declaration of Helsinki and its revisions when conducting scientific research. If a potential subject is minor or not capable of giving consent due

[56] Article III(1) and Article III(3) of the Constitution of Bosnia and Herzegovina, accessed February 19, 2024, https://www.ustavnisud.ba/uploads/documents/constitution-of-bih_1625734692.pdf.

[57] The Constitution of the Republic of Srpska, accessed February 17, 2024, https://www.narodnaskupstinars.net/sites/default/files/upload/dokumenti/ustav/eng/USTAV-RS_English.pdf.

[58] The Health Protection Law, Official Gazette of the Republic of Srpska, no. 57/2022.

[59] The Code of Medical Ethics and Deontology of the RS Medical Doctor's Chamber, accessed February 18, 2024, https://komoradoktorars.org/index.php/2018-11-26-17-31-48/s-l/d-s-dicins-i-i-d-n-l-gi.

to lack of legal capacity or their state of consciousness, consent is requested from their legal representative (Article VI(6)). The Code also stipulates that the physician should pay particular attention to the situations where the subject's ability to refuse consent is significantly compromised due to their reliance on the physician (Article VI(8)). The physician is obliged to present the research plan for assessment in terms of scientific and educational justification and ethical acceptability to the authorized institution (Article VI(3)).

In the FBiH, a federally organized entity, health protection regulation is one of the shared responsibilities of the Federation and its cantons[60] (the FBiH consists of ten federal units called cantons). According to Article 38(1) of the FBiH Law on Rights, Obligations and Responsibilities of Patients,[61] informed consent is required for medical and scientific research or clinical testing of drugs and medical devices on a patient, as well as including them in educational activities. In the case of minors or legally incompetent patients, consent is obtained from their parents, guardians or legal representatives while also taking into account the minor or legally incompetent patient's opinion (Article 38(3)). Under Article 38(5) of the Law, the legal provisions on the protection of persons with mental disorders are applied accordingly to the rights of patients with mental disorders who participate in research. According to Article 16 of the FBiH Law on Protection of Persons with Mental Disorders,[62] medical research on persons with mental disorders can only be undertaken if a person participating in the study has given written consent, the research is related to the treatment of a mental disorder experienced by that person, and the presumed risk of the research to the person with a mental disorder is not disproportionate to its benefit. If the person with mental disorders is unable to consent, the consent of the subject's legal representative is required.

60 Article 2 of the Constitution of the Federation of Bosnia and Herzegovina, Official Gazette of the Federation of Bosnia and Herzegovina, no. 1/94, 13/97, 16/02, 22/02, 52/02, 60/02, 18/03, 63/03, 9/04, 20/04, 33/04, 71/05, 72/05, 88/08.

61 The Law on Rights, Obligations and Responsibilities of Patients, Official Gazette of the Federation of Bosnia and Herzegovina, no. 40/2010.

62 The Law on Protection of Persons with Mental Disorders, Official Gazette of the Federation of Bosnia and Herzegovina, no. 37/2001, 40/2002, 52/2011, and 14/2013.

In 2009, the Agency for Medicinal Products and Medical Devices of BiH (ALMBiH) was established as "an authority responsible in the area of medicinal products and medical devices which are manufactured and used in medical practices in Bosnia and Herzegovina" (Article 3(1) of the BiH Medicinal Products and Medical Devices Act (MPMDA)).[63] The ALMBiH is responsible for registering and approving clinical trials of medicinal products and monitoring adverse effects occurring during clinical trials (Article 7(1)(d)). After local ethics committees established within the entity-level university clinical centres (or within other health institutions authorized to conduct clinical trials) approve a clinical trial application, it is submitted to ALMBiH for approval. The ALMBiH's committee for clinical trials, which consists of seven members, assesses documentation enclosed in the application for obtaining permission for clinical trials of medicinal products and the application for registering the clinical trial or an amendment or annex to the already registered and approved clinical trial protocol (Article 24 of the MPMDA). According to the Ordinance on Clinical Trials on Medicinal Products and Medical Devices,[64] if the candidate is incapable of giving personal consent for the participation in a clinical trial on the medicinal product, if they are not conscious or not capable of reasoning, the consent may be given by parents, guardians, legal representatives, spouse, and if the researcher believes that the participation may be useful for the well-being and interests of the research subject (Article 14(j)). If necessary, and under special precautions, a clinical trial may be conducted on minors suffering from a disease or from a condition for which the tested medicinal product is intended. Clinical trial that includes a minor may be conducted if: (1) a parent or legal guardian has given written consent (written consent should represent the presumed will of a minor and may be withdrawn at any time, without harm to them), (2) a minor has been provided with information that is understandable to them by a person who has experience in working with minors, and (3) written consent has been given without the encouragement to participate in a clinical trial (Article 15 of the Ordinance).

63 The Medicinal Products and Medical Devices Act, Official Gazette of Bosnia and Herzegovina, no. 58/2008.

64 The Ordinance on Clinical Trials on Medicinal Products and Medical Devices, Official Gazette of Bosnia and Herzegovina, no. 4/2010.

6. Conclusion

Medical research involving human subjects can enhance the well-being of individual patients and provide enormous social benefits. It enables the acquisition of new scientific knowledge and the development of novel therapeutic and diagnostic procedures but also raises significant ethical and legal issues. Particularly controversial is research on subjects who are incapable of consenting to the study or are in a position of subordination and more susceptible to manipulation and mistreatment. Such subjects are considered vulnerable and the object of special protection. Nevertheless, it is necessary to ensure access to medical research for vulnerable individuals and groups in order to enable them to benefit from it. The various forms of research subjects' vulnerability should be considered when regulating medical research.

The analysis of the legal framework of medical research in BiH (BiH entities) showed that it complies with basic international and European standards regarding protecting research subjects, including those who are incapable of consenting. However, some changes to the entity legislation are appropriate. One of the justified legislative changes in the RS would be the introduction of an assent requirement, while participation in the decision-making of research subjects incapable of giving consent should be more precisely regulated in the FBiH legislation.

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