


## Informed Consent in Clinical Studies in the Republic of Srpska


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**Abstract:** As human medicine is developing at a galloping pace, continuously offering new medical products, diagnostic methods and preventive programmes, there is almost no time gap between their creation and application in medical practice. All these biomedical achievements are primarily intended to improve public health and the patient's quality of life and health. Hence, it is important to define potential risks, side effects, and unwanted outcomes when applying a medical product/treatment before integrating it into healthcare. Unlike any other product/treatment intended for human use, medical products/treatments require prior clinical testing on human subjects (sick or sound). The authors of this paper have restricted their scientific interest to the participant (human subject) of a clinical study as one of the core elements of a clinical investigation, representing at the same time its means and its aim. By analyzing relevant international as well as national legal rules and ethical principles of the Republic of Srpska related to the participation of humans in clinical studies, it will be concluded that the participants' safety and right to self-determination, integrity, and autonomy manifested through their independent right to either consent or refuse to participate in a clinical study supersedes the interests of science or society. However, clinical trial-related

statistical data obtained from randomly chosen healthcare institutions in the Republic of Srpska will show certain derogations from prescribed ethical policies. Considering this fact, the authors have paid special attention to thematising the ethicality of recruiting participants for a clinical study based on partial or no information related to the purpose, methods, potential risks and side effects of the investigation in the name of the greater good for humanity. Such practice has accentuated the discretionary powers of ethical review committees on the one side and the uncertainty of the right to informed consent on the other.

## 1. Introduction

Clinical experiments/trials/investigations/studies on human subjects have always been justified as *ultima ratio* when all other methods or means of study could not yield results for the good of society. However, certain legal and ethical standards of medical behavior must be respected when the subject of clinical study is a human being. One of the basic requirements is voluntary informed consent<sup>1</sup> obtained from every participant before any clinical study.

Informed consent is not just the act of signing a confirmation form but rather a complex process of providing the participant with sufficient information about the nature, duration, and purpose of the study; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon health or person of the participant which may be the result of participation in the experiment.<sup>2</sup> All possible risks must be weighed against the expected benefits, and all unnecessary physical and mental suffering must be avoided. These Nuremberg standards for carrying out experiments on human subjects have been extended into general codes of medical ethics.

<sup>1</sup> About legal, ethical and clinical aspects of informed consent in all medical interventions, except clinical studies, see: Snežana Pantović and Dijana Zrnić, “Ethical, Clinical and Legal Aspects of Informed Consent in Montenegro, Republic of Srpska, Serbia and Croatia,” *International Scientific Conference: Challenges and Perspectives of the Development of Legal Systems in the XXI Century – Conference Proceedings* 1, no. 3 (2023): 115–33, <https://doi.org/10.7251/NSTT12301115P>.

<sup>2</sup> “The Nuremberg Code of 1947,” *British Medical Journal* 313, no. 7070 (1996): 1448.

The Republic of Srpska has formalized and accorded its principles and protocols related to clinical studies to the highest legal and ethical standards accepted worldwide, starting from the Nuremberg Code, the International Covenant on Civil and Political Rights of the United Nations, the Helsinki Declaration, the CIOMS Guidelines of 2002, the WHO Good Clinical Practice Guide of 1995, Guidelines for Good Clinical Practice (GCP) for Pharmaceutical Products of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use of 1996, the European Council's Convention of the Protection of the Human Beings with regard to the Applicant of Biology and Medicine: Convention on Human Rights and Biomedicine (1997, came into effect in 2009); the European Council's Additional Protocol to the Conventions on Human Rights and Biomedicine, considering Biomedical Research (2009); Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 (came into effect on 2004) on the approximation of the laws, regulations and administrative provisions of the Member States of Clinical Trials on medicinal products for human use; and all other rules and regulations related to clinical studies.

This study will primarily focus on the nature of Informed Consent in Clinical Studies in the Republic of Srpska and the extent of information provided to participants about the clinical study before they consent to any kind of clinical testing. In addition, the connection between risks and direct benefits to the participants will also be explored. In the process of analyzing legal and ethical solutions and recommendations, the authors intend to highlight any dilemmas or unpopular trends in clinical practice related to informed consent, such as engaging sick patients to avoid compensation and/or insurance obligations, (un)ethical recruiting of healthy individuals, breaching the minimal risk principle, etc.

It will be concluded that the Republic of Srpska healthcare regulatory system and ethical policies insist on fully informed consent before any clinical study, stressing the predominance of the protection and safety of human life and health over any scientifically and/or socially beneficial research results. Urgent situations and/or psychological stability of the participant, however, open the door to modifications of informed consent in the sense of allowing temporary retention of information from the participant in the recruiting process. The clinical practice has shown that, without a strict

review mechanism, these extraordinary situations will provide ample room for manipulations and unethical conduct of the investigators whose primary interest is not necessarily the safety and well-being of the participant.

## 2. The Concept of Informed Consent in a Clinical Study

### 2.1. Clinical Study

What is a clinical study? It is an investigation involving human subjects aiming at answering a specific medical question. A careful and quality clinical study is the safest way to discover new types of treatment and health improvement methods in humans. In oncology, for example, an interventional study analyzes whether a new/experimental treatment or a standard treatment applied in a new way is safer, more efficient and better under controlled conditions than the existing treatment. In other words, any investigation involving human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety and/or efficacy, can be termed a clinical study.<sup>3</sup> Most medications and other forms of treatment currently in use result from clinical studies confirming their efficacy.

Clinical studies are carried out by a study team comprised of a physician, medical nurse, and other healthcare personnel. Every clinical study is based on a detailed study plan (protocol) to ensure the safety of participants and the relevance of study results. The protocol, among other things, anticipates eligibility criteria for the participants (inclusion and exclusion criteria), diagnostic testing plan, medicinal application procedure, and study duration.

Well-designed clinical studies are highly beneficial for patients, who can thus actively contribute to their treatment by gaining access to the latest modes of treatment before they become widely applicable. They represent other patients diagnosed with a similar disease and voluntarily contribute

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<sup>3</sup> Section 1.12 of Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (R2) (2016).

to advancing medical science. Usually, the participants are divided into experimental and control groups. The experimental group receives a new medical product/treatment, while the control group receives a standard treatment or placebo. The control group helps compare the research results with the current standard.

Clinical studies are carried out in phases. First, there is a preclinical phase, which implies *in vitro* and *in vivo* testing on animals. Then, a clinical study follows, which can be divided into four phases (I–IV). The first phase implies an investigation involving a small cluster of healthy individuals (usually 20–80). If the product/treatment is effective, the number of participants will increase in every following phase. The recruitment procedure is gradual to ensure the safety of the participants.

Clinical studies can be funded by various organisations or individuals, such as physicians, healthcare institutions, consortiums, voluntary groups, pharmaceutical companies, or state agencies. The financial component plays a crucial role in performing clinical studies. Unfortunately, promising medical treatments/products are stopped in the preclinical phase without sufficient sponsorship. More often than not, clinical studies are dictated by the financial interests of stakeholders, such as pharmaceutical companies, rather than by altruism. The Gajić family case stands well in support of this argument. This family from Banja Luka (Republic of Srpska), whose two daughters suffer from Lafora disease, is the biggest donor to Lafora disease research worldwide. However, since the number of people (primarily children) suffering from this disease is insignificant, few pharmaceutical companies are interested in funding a clinical study of a new therapeutic strategy developed at the Toronto University Laboratory.<sup>4</sup> Hence, the future of Lafora patients very much depends on the benevolence of willing private donors and the fundraising campaigns of their families.

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<sup>4</sup> On Lafora disease and the Gajić family, see a documentary, *The Faces of Lafora* (2017), directed by Denis Bojić, <https://www.youtube.com/watch?v=EP7OIQBN1jY>; on a new therapeutic strategy for Lafora disease, see: Rashmi Parihar and Subramaniam Ganesh, “Lafora Progressive Myoclonus Epilepsy: Disease Mechanism and Therapeutic Attempts,” *Journal of Biosciences* 49, no. 22 (2024): 1–15; Felix Nitschke et al., “Lafora Disease – From Pathogenesis to Treatment Strategies,” *Nature Reviews Neurology* 14 (2018): 606–17, <https://doi.org/10.1038/s41582-018-0057-0>.

Next to qualified investigators, eligible participants, and willing sponsors, clinical studies depend on material and technical resources, which are relatively scarce in low and middle-income countries/regions, such as the Republic of Srpska. In resource-limited populations, numerous barriers exist to prevent clinical study design and implementation. Commonly cited examples are lack of infrastructure, heterogeneity of resource availability among countries, unfamiliarity with clinical study regulations, cultural/ethical issues, and other legal and administrative constraints around data-sharing.<sup>5</sup> Few healthcare facilities in the Republic of Srpska meet the set-up requirements for performing clinical research on humans due to unreasonably strict and complex government regulatory systems, unnecessary delays in ethical approval procedures, and meagre government funding.

## 2.2. Informed Consent in a Clinical Study

Clinical studies performed on human subjects carry greater risk to the life and health of the participants, requiring stricter subject-oriented regulatory policies. Thus, voluntary informed consent has become the central institute of international and national legal and ethical guidelines that regulate clinical studies. The main difference between a clinical study and a medical treatment subject-wise is that a study participant is considered “a subject of research” and not a patient. Their consent to participation in a clinical study must be based on fair and objective, even if unpromising, information about the nature and outcome of the study. To that end, before signing the ICF, the subject of research must be made aware of the nature, objectives, benefits, implications, risks, and inconveniences of the clinical study; the subject’s rights and guarantees regarding their protection, especially the right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical study is to be conducted, including the expected duration of the subject’s participation in the clinical study; and the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical study is discontinued.<sup>6</sup>

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<sup>5</sup> Surbhi Grover et al., “Clinical Trials in Low and Middle-Income Countries – Successes and Challenges,” *Gynecologic Oncology Reports* 19 (2017): 5–9.

<sup>6</sup> Chapter V, Article 29, Regulation (EU) 536/2014.

Research subjects may gain some personal treatment benefits from participating in a clinical study. However, they must understand that they may not benefit from the clinical study; they may be exposed to unknown risks, and their participation is voluntary. Therefore, they must be given sufficient time to consider the risks and benefits of participating in a clinical study before giving their voluntary consent. In addition, potential subjects must be given ample opportunity to enquire about details of the trial, and they must not be “lured” into consenting by false or incomplete information related to the study.<sup>7</sup>

### 2.3. Legal Aspects of Informed Consent in a Clinical Study

The recorded history of the first clinical studies goes back to the Biblical descriptions in 500 BC.<sup>8</sup> In the early evolutionary period, studies were usually concerned with dietary therapies. Still, as soon as the basic approach of the clinical study was defined in the 18th century, efforts were made to refine the design and statistical aspects. These were immediately followed by changes in the regulatory and ethics milieu.<sup>9</sup> However, only after the 1947 judgment by the War Crimes Tribunal at Nuremberg was a new set of standards of ethical medical behavior for the post-World War II human rights era established. Among other requirements, the Nuremberg Code verbalises the requirement of *voluntary informed consent* of the human subject. The principle of voluntary informed consent protects the right of the individual to control their body. That meant that the participant should have the legal capacity to give consent; they should be so situated as to be 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; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable them to make an understanding and enlightened decision. This means that before giving consent, the participant must be well informed about the nature, duration,

<sup>7</sup> Para. 3.3a of WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, *WHO Technical Report Series*, no. 850 (1995), Annex 3.

<sup>8</sup> Roger Collier, “Legumes, Lemons and Streptomycin: A Short History of the Clinical Trial,” *Canadian Medical Association Journal* 180, no. 1 (2009): 23–4.

<sup>9</sup> Arun Bhatt, “Evolution of Clinical Research: A History Before and Beyond James Lind,” *Perspectives Clinical Research* 1, no. 1 (Jan–Mar 2010): 6–10 (6).

and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon their health or person which may possibly come from their participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. During the experiment, the human subject should be at liberty to bring the experiment to an end if the subject has reached the physical or mental state where continuation of the experiment seems impossible.<sup>10</sup>

This Code also recognizes that the risk must be weighed against the expected benefit and that unnecessary pain and suffering must be avoided. The doctors should avoid actions that injure human patients and should terminate the experiment when its continuation is likely to result in injury, disability, or death to the experimental subject. Every participant must be aware of the possible risks of side effects and unwanted events during the clinical study and that the experimental treatment may be ineffective for certain participants.

The Nuremberg set of guidelines on medical/clinical research on humans soon became an integral part of the International Covenant on Civil and Political Rights of the United Nations, prohibiting the participation of a human subject in a clinical study without their free consent (Article 7).<sup>11</sup> The Helsinki Declaration also places special attention on the informed consent principle. Hence, Article 24 states that any medical research on human subjects requires the researcher to adequately inform the participant about the study's purpose, methods, and anticipated benefits and potential risks, including its inconveniences.<sup>12</sup> However, the Declaration allows for the study involving human subjects without their informed consent as long as the physical or mental condition that prevents them from consenting is a necessary characteristic of the studied population (Article 29).

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<sup>10</sup> Nuremberg Code (1947).

<sup>11</sup> United Nations Covenant on Civil and Political Rights, 1967, accessed February 5, 2024, [https://treaties.un.org/doc/Treaties/1976/03/19760323%2006-17%20AM/Ch\\_IV\\_04.pdf](https://treaties.un.org/doc/Treaties/1976/03/19760323%2006-17%20AM/Ch_IV_04.pdf).

<sup>12</sup> World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, WMA General Assembly, Helsinki, Finland, June 1964 and amended in 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, and 2013.



CIOMS Guidelines of 2002 are more flexible in comparison to the Helsinki Declaration in terms of the request for informed consent by giving discretionary rights to ethics committees to decide about exceptions from this fundamental principle. Thus, according to Guideline 4, in all biomedical research involving humans, the investigator must obtain the voluntary informed consent of the prospective subject or a legally authorized representative per applicable law. The decision to participate in research must be made by a competent individual who has received the necessary information, has adequately understood the information, and has arrived at a decision without having been subjected to coercion, undue influence, inducement, or intimidation. A competent individual is entitled to freely choose whether to participate in research. Thus, informed consent protects their freedom of choice and respects their autonomy. In case an individual has limited capacity to give adequate informed consent (young children, adults with mental or behavioral disorders, and individuals unfamiliar with medical concepts and technology), their decision is complemented by an independent ethical review committee (Guidelines 13, 14, 15). The prospective subject's ability to understand the information necessary to give informed consent depends on their maturity, intelligence, education, and belief system. They should be given sufficient time and resources to reach a decision. As a general rule, the subject should sign a consent form before participating in research. Exceptionally, the ethical review committee may approve a waiver of the requirement of a signed consent form if the research carries no more than minimal risk attached to routine medical or psychological examination. This means that waiver of informed consent is to be regarded as unorthodox and exceptional and must, in all cases, be approved by an ethical review committee.<sup>13</sup>

Intending to set up general standards for performing biomedical research on humans, the WHO approved the Good Clinical Practice Guide in 1995, thus acknowledging the legal and ethical principles of the Helsinki

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<sup>13</sup> Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002): Guideline 4, accessed February 5, 2024, [https://ec.sut.ac.th/File/pdf/1%202\\_CIOMS\\_Guidelines\\_2002.pdf](https://ec.sut.ac.th/File/pdf/1%202_CIOMS_Guidelines_2002.pdf).

Declaration and CIOMS Guidelines.<sup>14</sup> Next to highlighting the voluntary and entirely consensual nature of participation in a clinical study, the GCP Guide also appeals to careful consideration of obtaining informed consent from certain groups of people whose participation is (un)justly motivated by expectations of benefits or a retaliatory response from senior members of the hierarchy in case of refusal to participate. Those are primarily members of a group with a hierarchical structure, such as medical, pharmacy, and nursing students, hospital and laboratory personnel, pharmaceutical industry employees, and armed forces members. Other vulnerable groups whose consent also needs special consideration include patients with incurable diseases, people in nursing homes, prisoners or detainees, the unemployed or people with a very low income, patients in emergency departments, some ethnic and racial minority groups, the homeless, nomads, and refugees. The process of recruiting should be carefully reviewed by the ethical review committee.<sup>15</sup> In addition, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in 1996, introduced the Guideline for Good Clinical Practice to ensure recognition of collected data from clinical studies by the regulatory authorities in the EU, Japan, and the USA. Hence, Article 2.9 states that “Freely given informed consent should be obtained from every subject prior to clinical trial participation.” Furthermore, Article 4.8.10 itemizes all the necessary information that the participant (human subject) should be provided with through informed consent discussion and the written informed consent form. In comparison to informed consent in other medical treatments, the Guideline provides for, in Article 4.8.11., a higher level of transparency and protection of the participants’ integrity by allowing them to:

receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.” Furthermore, during the subject’s participation in the study, their legally acceptable representative

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<sup>14</sup> World Health Organisation Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, WHO Technical Report Series, no. 850, 1995, Annex 3.

<sup>15</sup> WHO GCP Guide, para. 3.3.

“should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.”<sup>16</sup>

According to the Oviedo Convention and its Protocols,<sup>17</sup> informed consent is not defined as an unconditional right, having been limited by the interest of public safety, the prevention of crime, the protection of public health or by the protection of the rights and freedoms of others (Article 26(1)). Those are, however, exceptional circumstances that rarely derogate the predominantly humanistic policy of the Convention, which is the protection of the physical and mental integrity and identity of a human being.

## 2.4. Ethical Aspects of Informed Consent in a Clinical Study

Every medical or clinical study that includes human participation should be designed and conducted to achieve scientific integrity and follow ethical principles to protect its participants' health, safety, and well-being.<sup>18</sup> Hence, defining specific criteria when planning a clinical study is important. Various ethical standards and guidelines guarantee the protection of safety, dignity, self-determination, and confidentiality of research participants' personal information. The ten-point Nuremberg Code emphasizes the importance of sound scientific research protocol and informed consent. These criteria include the selection of patients who will participate in a concrete clinical study. A fundamental principle of clinical study is inclusion and exclusion criteria that enable the plausibility of research results. Factors that enable participation represent inclusion criteria, while a person who meets certain exclusion criteria cannot participate in a clinical study. These factors are, among others, age, sex, type and severity of disease, earlier treatment, and other medical conditions/diseases. It is important to note that inclusion and exclusion criteria are not intended to disable participation in a clinical study based on personal reasons but to identify a group of patients

<sup>16</sup> Pantović and Zrnić, “Ethical, Clinical and Legal Aspects,” 125.

<sup>17</sup> European Council's 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 (ETS No. 164) and its Protocols, Oviedo, 4 April 1997, entered into force 1 December 1999, accessed February 6, 2024, <https://www.coe.int/en/web/bioethics/oviedo-convention>.

<sup>18</sup> Hyoungh Shin Lee, “Ethical Issues in Clinical Research and Publication,” *Kosin Medical Journal* 37, no. 4 (2022): 278–82, <https://doi.org/10.7180/kmj.22.132>.

who stand the best chance of successful treatment and to provide the safety of applied therapy. In addition, well-defined criteria help investigators get a clear answer to the study question. With that in mind, a patient can withdraw from further participation in a clinical study at any time. It is sufficient to inform the assigned investigator about the decision and the reasons for dropping out. Although modern research ethics developed with the primary aim of protecting the safety and integrity of the participant, introducing strict scientific research protocols and informed consent, several reports on unethical medical studies conducted without informed consent on vulnerable research participants have been published since the early 1960s.<sup>19</sup>

### 3. Informed Consent in Clinical Studies in the Republic of Srpska

#### 3.1. General Overview

The Republic of Srpska is a region where healthcare professionals work in environments with limited medical, human, and surgical resources. Such a setting greatly affects the research opportunities that involve human subjects. Although their legal and ethical guidelines closely follow the requirements and recommendations of various international medical and human rights associations (World Health Organisation, International Medical Association, United Nations, etc.) concerning clinical studies, still the double burden of disease in this lower-income region stresses a strong need for cost-effective and novel treatment plans that will be based on sustainable health research capacity.<sup>20</sup> Next to the legality of clinical studies performed in the Republic of Srpska that involve human subjects, there is the question of the ethicality of human experimentation that requires fully informed consent from research subjects. To that end, the authors of this paper share their scepticism with American anaesthesiologist Henry Beecher, who, back in 1966, welcomed the attempts of the federal government to insist on obtaining consent from research subjects as a worthy and necessary ideal but found that “obtaining consent in any fully informed sense was

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<sup>19</sup> Henry K. Beecher, “Ethics and Clinical Research,” *Bulletin of the World Health Organization* 79, no 4. (2001): 367–72.

<sup>20</sup> Such objectives are set up in the Quality Policy of UCC RS no. PM-06–002 of 15 September 2014.

highly unrealistic”.<sup>21</sup> Instead, Beecher argued that the presence of an intelligent, informed, conscientious, compassionate, and responsible investigator offered the best protection for human research subjects.<sup>22</sup> In light of controversies that surround the voluntary participation of human subjects in clinical studies based on their informed consent or lack thereof, which are, according to Beecher, of universal nature, the authors will point out the most common legal and ethical challenges faced by both, investigators and study participants in the process of obtaining voluntary informed consent in the Republic of Srpska.

### 3.2. Informed Consent in Clinical Studies in the Republic of Srpska

As a low-income region, the Republic of Srpska invests insufficiently in public healthcare protection programmes, including biomedical research, to benefit science and society.<sup>23</sup> The budget for improving the quality of healthcare protection in the Republic of Srpska for 2024 amounts to KM 1.6 million (approx. EUR 750,000).<sup>24</sup> For comparison, neighboring Serbia, placed among lower-income countries, has become a land of opportunity for clinical research, with 322 clinical trials currently conducted inside its borders (oncology 68, gastroenterology 42, neurology 38, and cardiology 36).<sup>25</sup> International sponsors are responsible for 84% of ongoing trials. According to the Cromos Pharma report, reasons for recognizing Serbia as

<sup>21</sup> Jon Harkness, Susan E. Lederer, and Daniel Winkler, “Laying Ethical Foundations for Clinical Research,” *Bulletin of the World Health Organization* 79, no. 4 (2001): 365–66.

<sup>22</sup> Ibid.

<sup>23</sup> For new drugs and treatment development in low- and middle-income countries/regions, see: Rakesh Jalali et al., “Drug Development in Low- and Middle-Income Countries: Opportunity of Exploitation?,” *American Society of Clinical Oncology Educational Book* 42 (2022): 1–10; Grover et al., “Clinical Trials,” 5–9; Adeel Khoja, Fiyah Kayim, and Naureen Akber Ali, “Barriers to Conducting Clinical Trials in Developing Countries,” *The Ochsner Journal* 19, no. 4 (2019): 294–5.

<sup>24</sup> Budget of Republic of Srpska for 2024, National Assembly of Republic of Srpska, accessed February 11, 2024, <https://www.narodnaskupstinars.net/?q=la/akti/bud%C5%BEet/bud%C5%BEet-republike-srpske-za-2024-godinu>; Ljiljana Kovačević, “New Distribution of RS Budget: Planned Destruction of Healthcare, Culture, and Education,” *Žurnal*, November 6, 2023, accessed February 11, 2024, <https://zurnal.info/clanak/plansko-unistavanje-zdravstva-kulture-i-obrazovanja/26383>.

<sup>25</sup> Data obtained from [clinicaltrials.gov](https://clinicaltrials.gov).

a promising clinical research destination are multiple, starting from high recruitment rates and vast patient population (8.6 million inhabitants); moderate research costs and investigator fees; high-quality standards of clinical research; high-quality, accredited research units tailored to clinical trials; well-qualified, compliant, and experienced staff of GCP-certified investigators; enhanced regulatory framework and validated safety guidelines under Serbian law and the Medical Devices Agency; an increasing and ever-improving business infrastructure for clinical trials, including advancing medical devices; an opportunity to participate in clinical trials allows Serbian patients to have access to novel biologics, which are still limited under the state-funded supply programs, furthering the motivation.<sup>26</sup>

Compared to Serbia, it is unrealistic for the Republic of Srpska to expect any professionalism in clinical research that would result in a new or improved medical product/treatment. Without adequate investment in biomedical research and biotechnological innovations, it is difficult to expect continuous improvement in the quality and safety of healthcare protection.<sup>27</sup> In the past four years (2020–2023), only a few clinical studies were undertaken, usually non-interventional and non-invasive, representing little to no risk to the human subject, by an internal medical professional for scientific purposes (academic career advancement), while others were sponsored by external partners.<sup>28</sup> Due to resource limitations, many of these studies were enabled by engaging patients for their personal benefit (mostly terminally ill patients) or obtaining consent from the study subject based on selective and limited information. These observations are only

<sup>26</sup> Cromos Pharma is an agency which offers partnership in international clinical research projects. Hence, it launches clinical trials in the US, Central, Eastern Europe, Central and South-western Asia. It is interesting to note that Bosnia and Herzegovina (RS) is not among European destination countries (Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia, Slovak Republic, Slovenia, Türkiye, Ukraine). “Serbia – A Land of Opportunity for Clinical Research,” November 29, 2022, accessed April 2, 2024, <https://cromospharma.com/serbia-a-land-of-opportunity-for-clinical-research/>.

<sup>27</sup> Articles 11, 16 (21) of the Healthcare Protection Act (Official Gazette of Republic of Srpska, no. 57/22).

<sup>28</sup> According to the UCC RS Ethics Board Decision no. 01–19–65–2/24 of 14 February 2024, 79 clinical studies were performed on adult patients treated at the UCC RS from 2020 to 2023, and all were sponsored by an external partner (usually, pharmaceutical companies).

partially supported by documented facts since access to statistical data concerning clinical studies in the Republic of Srpska was either delayed or denied by the ethics boards/committees of healthcare institutions in charge of granting clinical studies on human subjects. However, unofficial statements from study participants and medical staff revealed many controversies regarding normative/ethical rules and principles and clinical practice.

### 3.2.1. Legal Aspects of Informed Consent in Clinical Studies in the Republic of Srpska

According to healthcare legislation of the Republic of Srpska, no clinical study can be performed without informed consent from the study subject, their guardian, or a legal representative. It is a fundamental legal and ethical requirement imposed on the investigator before conducting any human experiment. Henceforth, only a mature patient with legal capacity can participate in a clinical study after providing informed consent in writing. If the patient is a child or a person without legal capacity, written consent is provided by their parent, guardian, or legal representative.<sup>29</sup> The patient can provide their consent only after being informed about the purpose, procedure, expected results, possible risks, and unwanted outcomes of a clinical study. We see that the quality of information (e.g. fullness, sufficiency, adequacy, etc.) is not precisely defined, leaving the investigator the discretionary right to make casuistic estimates as to the quantity and quality of information sufficient to convince the subject to participate in a clinical study. Such normative imprecision as to the quality of information provides ample room for the unethical approach of the physician to the study patient, who, based on trust, will agree to virtually any request their physician may make. However, no patient is ready to jeopardize their health or risk their life for the sake of science, especially if it requires trying something no one knows would work.

A senior investigator must inform the potential study subject in writing about their right to refuse to participate in a clinical study and the right to terminate their participation at any time. This legal imperative can be interpreted as *in favorem vitae*, which means that the life and health of a human subject are more important than achieving results in clinical research. A human subject who suffers harm, damage, or loss at the expense of participating in a clinical study has a right to compensation. This

<sup>29</sup> Article 52 (1), (2) of HCPA RS.

means that the subject's consent does not have an *absolute* value and does not relieve the investigator from liability. However, there is a fine line between the subject's informed consent and the legal principle of *volenti non fit iniuria*. The most concrete legal ground for seeking informed consent arises from a contractual relationship between the subject and the investigator (ICF), preceded by the investigator providing *necessary* information to the subject. As a contracting party, the study subject is entitled to a copy of the signed ICF. Under the same Act, patients undergoing any other medical treatment/intervention are denied this right, indicating awareness of higher transparency of the study process. In addition, the RS legislator has restricted the patient's participation in a clinical study to drugs and medical assets, acting as *lex specialis* in relation to the Drugs and Medical Assets Act of Bosnia and Herzegovina as *lex generalis*.<sup>30</sup>

Key barriers that impede the study process are the lack of financial resources and skilled personnel, as well as regulatory and administrative issues. Accordingly, most funding for clinical studies comes from pharmaceutical companies established in the West.<sup>31</sup> The lack of qualified personnel is also apparent. Individuals with specialised training or experience in clinical studies often prefer to work abroad due to better opportunities, resulting in a continuous brain drain in the Republic of Srpska. Every request for a clinical study must be approved by the ethics board of the respective state-owned healthcare institution, which has developed a set of rules and guidelines to further arrange clinical studies.<sup>32</sup> Thus, for example, the University Clinical Centre of the Republic of Srpska (UCC RS) has adopted the Rulebook on the Performance of Clinical Studies (2016), which is accorded with the Rulebook on Clinical Study of Drugs and Medical Assets of Bosnia and Herzegovina<sup>33</sup> and Guidelines on Good Clinical Practice in Clinical Studies of BiH,<sup>34</sup> and is based on ethical and legal regulations of RS (BiH) and the international guidelines, such as the RS Healthcare Protection Act, the RS Social Welfare Act, the RS Records and

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<sup>30</sup> Article 52 (9) of HCPA RS.

<sup>31</sup> Semi-official data obtained from the Ethical Committee of the Ministry of Health and Social Welfare of RS; email dated 12 February 2024.

<sup>32</sup> Article 52 (3–11) of HCPA RS.

<sup>33</sup> Official Gazette of Bosnia and Herzegovina, no. 4/10.

<sup>34</sup> Official Gazette of Bosnia and Herzegovina, no. 19/12.



Statistical Research in Healthcare Protection Act, the Rulebook on Clinical Studies of Drugs and Medical Assets of BiH, the Code of Medical Ethics of PHI University Clinical Centre RS, the Code of Ethics for Nurses/Medical Technicians of PHI UCC RS, the Healthcare Protection and Safety at Work Policy of PHI UCC RS, and the Quality Policy of PHI UCC RS. However, unnecessary delays in ethical approval procedures and complex and unreasonably strict government regulatory systems turn informed consent into a mere formality.

Another legal loop that stands in the way of transparent and fair clinical research is the discretionary right of competent ethical authorities to decide *in meritum* when informed consent is not needed for the patient to participate in a clinical study, thus opening the door to manipulation with the requirement of full information before consenting to a clinical trial.

### 3.2.2. Ethical Aspects of Informed Consent in Clinical Studies in the Republic of Srpska

Medical research involving human subjects should be based on truth, promote and demonstrate scientific integrity, and follow ethical standards and guidelines to protect the study participants. Furthermore, the publication of clinical studies should be transparent and accessible to the general public. The investigator must possess full knowledge of ethical issues related to voluntary, informed and consensual participation of the participant in the clinical study to avoid misconduct allegations. Bound by the ethical principles of the Declaration of Helsinki, international ethical guidelines of biomedical research on humans, a clinical investigator in the Republic of Srpska must understand, respect, and protect the autonomy of will of the subjects, their right to self-determination and dignity, as well as the standards of good clinical practice set up to ensure and safeguard the safety and well-being of the patients and the authenticity of the study results.<sup>35</sup>

Most clinical studies in the Republic of Srpska are carried out on sick patients treated at the research healthcare institution.<sup>36</sup> According to the Rulebook, study participants should be tested with a new drug or medical asset intended to treat the patient's life-threatening primary disease.<sup>37</sup>

<sup>35</sup> Article 3 of the Rulebook on Clinical Studies, PHI UCC RS.

<sup>36</sup> Semi-official data obtained from the Ethical Committee of the Ministry of Health and Social Welfare of RS, email dated 12 February 2024.

<sup>37</sup> Article 4 of the Rulebook.

Due to the patient's already compromised health and previously obtained informed consent, it is very difficult to question the ethicality of the study procedure in relation to the voluntariness of the patient's participation. Furthermore, if there are unwanted effects on the patient's health due to the research therapy, it would be challenging to prove that the patient was not sufficiently informed about all the possible risks before giving consent. As mentioned before, publications of clinical studies are generally not transparent, the exception being scientific articles and theses in medicine, and the population interested in the study results cannot have open access to the study reports, contrary to the standard of publicity and transparency of clinical studies adopted by the ethics boards/committee of the Republic of Srpska research healthcare institutions and the Ministry of Health and Social Welfare.<sup>38</sup> Therefore, the authors have only managed to access fragmentary statistics about clinical studies carried out in healthcare institutions in the Republic of Srpska. Such a non-transparent policy prevents science and society from improving. Furthermore, unsatisfactory access to information about clinical trials largely affects the successful enrolment of participants into trials, especially those who volunteer for research. The right to information and informed consent in a clinical trial is a shared challenge among the neighboring countries, including Croatia. Although integrated into the EU, Croatia is still struggling with transparency of clinical trials, with the fewest registered trials in the EU Clinical Trials Registry (196 in 2017). This is the conclusion of Šolić et al., who assessed the transparency of clinical trials from the data available in the public domain and conducted an anonymous survey on a convenience sample of 257 patients. The authors further identified the possibility of benefiting from a new treatment as one of the main reasons Croatian patients participate in clinical studies. As for the negative practice of patients refusing to participate, the most prominent reasons are the fear of being a human guinea pig, worries they will be in the control group receiving a placebo and be thus left without help, and the feeling that joining a clinical trial means that all hope is lost. One of the problems contributing to this distrust is the lack of understanding of the methodology of clinical trials

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<sup>38</sup> Article 29(4) of the Rules of Procedure of the Ethical Committee, Ministry of Health and Social Welfare of the Republic of Srpska, no. 11/04–052–8/17 of 16 March 2017.

and their purpose despite the information received during the informed consent procedure.<sup>39</sup>

Faced with the problem of open access to information, the authors had to concede to the data found in the public domain. Thus, having access to the online list of doctoral theses in research medicine defended at the Faculty of Medicine Banja Luka University (2020–2023), the authors selected six doctoral theses based on human clinical research.<sup>40</sup> Two theses resulted from an observational clinical study that required access to medical records of patients treated at the UCC RS. In one thesis, the investigator mentions that the request for performing a clinical study has been reviewed and granted by the Ethics Board of the UCC RS. Still, he does not list informed consent as one of the inclusion criteria, which is one of the essential requirements for the approval of the clinical study by ethics boards. The second thesis, however, includes informed consent among the inclusion criteria and its lack in the exclusion criteria. It is to be concluded that there is a notable conflict between the good clinical practice guidelines that allow for the exclusion of informed consent if the clinical study is based on analyzing statistical data and registers and the right to the confidentiality of research participants' personal information.

The remaining four theses were based on interventional clinical research. One included ten healthy subjects (control group) and 60 sick patients (experimental group). It was stated in the thesis that the participants were informed orally and in writing about the study protocol and the purpose of the research, and they confirmed their voluntary participation by signing the ICF. Based on the subject of the study (effects of the extract from the pomegranate peel on diabetes treatment), it is to be assumed that neither healthy nor sick participants were compensated for their voluntary engagement, and they were not insured against possible risks to their health. The authors have a valid reason to believe in the correctness of such an assumption, knowing that the investigator who initiates a clinical study

<sup>39</sup> Ivana Šolić et al., "Transparency and Public Accessibility of Clinical Trial Information in Croatia: How It Affects Patient Participation in Clinical Trials," *Biochemia Medica* 27, no. 2 (2017): 259–69, <https://doi.org/10.11613/BM.2017.027>.

<sup>40</sup> The analyzed doctoral dissertations can be found on [https://unibl.org/sr/vesti?q\[by\\_kategorije\]\[\]=12](https://unibl.org/sr/vesti?q[by_kategorije][]=12), accessed February 14, 2024.

for academic advancement is usually not adequately funded. Hence, the investigator has to count on the patients' goodwill to contribute to science without compensation. In such cases, the investigators must be well aware that the burden of responsibility lies entirely on them and that they should not abuse the relation of trust that they create with the patients. The practice has shown that participants who are harmed due to participation in a clinical study seldom take any legal action against the investigator, but their trust in the healthcare system is shattered.<sup>41</sup>

The remaining three theses also confirmed that they obtained an ethics board approval to carry out the clinical study. Still, knowing the requirements for obtaining the approval, IC being one of them, we cannot but notice certain inconsistencies in the research information that does not include informed consent in the inclusion criteria or does not reveal the process of recruiting participants. Likewise, the authors could not but notice the formal aspect of informed consent by carefully reading the recruitment protocol in the studied theses. Hence, in one thesis, it was stated that the candidates were first orally introduced to the purpose and aim of the subject research, and thus their verbal consent was obtained. Then, the candidates were given an informed consent form to read, understand, and sign, which they eventually did. It cannot be expected that an average person will fully understand the complexities and risks of medical research without the investigator's thorough and detailed explanation. Patient knowledge and awareness of and participation in clinical studies may be a special problem for smaller research communities such as the Republic of Srpska. There is little information on how well patients are informed about clinical trials in the Republic of Srpska. However, judging from the experience of low awareness of and adherence to common medical procedures among RS patients, a high level of information about clinical research, its risks and effects cannot be expected.

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<sup>41</sup> A case of a pregnant woman (identity known to the authors) who was invited to participate in a clinical study whose purpose was to define the stability of sugar values in pregnancy and who was informed by the investigator that there was no risk to her or her baby's life or health, but eventually resulted in unnecessary stress (the level of sugar in her blood was read as abnormally high, due to technical error of the test equipment) confirms the scepticism in the consent being obtained in the fully informed sense.

#### 4. Conclusion

As a low-income region, the Republic of Srpska human research medicine struggles with many legal, social, personnel, economic, and ethical challenges. The investigators have a legal and moral obligation to respect and protect the safety and interests of the study participants, which implies fully informing the study subject of the nature, duration, purpose, methods, inconveniences, risks, and effects of the study. However, imprecision in legal defining the quality of information has enabled the supremacy of the investigator's discretionary over the subject's consent based on full and objective information. Clinical research can only be conducted when the objective outweighs the participant's risk.

The first level of protection of the subject's interests should be the investigator, through an open, sincere and responsible approach in the informing process, which does not stop with obtaining the subject's informed consent but lasts throughout the clinical study. By law, the surveillance pyramid starts with the investigator, continues to the ethics board and ends with the ethics committee. However, such a legal setting is severely ignored and nonfunctional. In addition to legal enforcement weaknesses, research medicine in the Republic of Srpska faces a very tedious red tape of unnecessarily strict regulatory mechanisms, including unreasonably delayed ethical approval procedures and non-transparency of study publications.

Meagre funding of clinical studies in the Republic of Srpska represents an open call to trained and skilled investigators and researchers to invest their knowledge elsewhere, reducing the study opportunities for the benefit of the Republic of Srpska population, thus impeding the advancement of healthcare protection in the Republic of Srpska. In opposition to overregulation stands non-regulation of certain research medical fields, such as healthcare technologies, reducing the scope of clinical studies to drugs and medical assets.

Currently, most clinical studies in the Republic of Srpska are funded by pharmaceutical companies based in the West, who show interest in placing their medical products in the Republic of Srpska healthcare market at unaffordable costs. On the other hand, Republic of Srpska researchers, faced with a severe shortage of funding and pressed by the requirements of academic advancement, find themselves in the position to either give up

on their academic careers (which they rarely do) or to risk their subjects' health or life by not presenting them with the "worst" possible scenarios, but instead showing them the variety of problems encountered to obtain their consent. However, according to the Republic of Srpska laws, even when informed consent has been obtained, it does not have absolute value; it does not relieve the investigator of any responsibility, which appears fair for obtaining consent without providing complete and objective information to the study subject.

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