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Legal Aspects of Protecting the Life and Health of Human Subjects in Biomedical Research

Clinical trials are the most expensive yet strategically crucial segment of the pharmaceutical market. Before getting to the market, a drug always passes an overall research that takes, according to Deloitte[2], about 14 years; still, the chances for the drug to be approved for production are only 4.1%. True, preclinical trials help to obtain insights whether further drug development is practical; nevertheless, clinical trials are still a decision-making phase. The latter reveals drug efficacy and safety for a human being through the research of pharmacodynamic, pharmacokinetic properties, side effects, etc. A distinctive feature of such research is, as mentioned above, mandatory participation of human subjects, since the findings of preclinical trials in vitro or in animals cannot be reliably extrapolated.

In the Russian Federation, clinical trials of "medications are conducted.... in accordance with the good clinical practice" reflected in the national standard (hereinafter referred to as GOST) "GOST R ISO 14155-2014[3]. National standard of the Russian Federation. Clinical trials. Good clinical practice". It is worth noting that this standard is almost a literal translation of the Good Clinical Practice (hereinafter referred to as GCP), the international scientific and ethical standard governing research involving human subjects, which in turn helps Russian researchers to integrate into the international academic community and share the findings of clinical trials.

In 2016 alone, the Ministry of Health of the Russian Federation issued 897 clinical trial authorizations[4]. The scale of research sparks a particular interest in the protection of trial subjects' rights, since the interests of sponsors/ researchers and participants in biomedical research are multidirectional. A. P. Grunenko was right: "The very nature of researcher-subject relationships is as follows: the top priority for the former is to obtain insights, for the latter, naturally, – to improve health. This, of course, is not about the cruelty, malice or lack of empathy of researchers, but about a real conflict of interests that raises a number of legal, ethical and deontological concerns[5]".

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[2] Getting drug to the market takes approximately 14 years [Electronic resource]. – URL: http://pharma.net.ua/publications/articles/16892-vyvod-novogo-lekarstvennogo-preparata-na-rynok-obhoditsja-farmkompanii-v-15-mlrd-i-zanimaet-14-let

[3] GOST R ISO 14155-2014. Clinical trials. Good clinical practice. Amended on 01.0672016 // Law reference system "Consultant- Plus"

[4] Barmanova E.U., Afonchikov U. V., Rogov E.S., Trubachev Y. M.. Monitoring of clinical trials as tool for providing quality of medicine // Vestnik Roszdravnadzora. 2015. № 6. P. 24-30.

[5] Grunenko A. P. Legal base of clinical trials // Medical law. 2003. № 1. P. 50-54.

The above mentioned both confirms the vulnerable position of subjects connected with the risk to their life and health in the course of clinical trials, but also, in turn, creates the need for proper statutory regulation of mechanisms protecting the rights of volunteers.

The existing laws on clinical trials seek to safeguard the rights and interests of human subjects. The cornerstone that forms the basis of legal regulations is the Article 21 of the Constitution of the Russian Federation that states that "no one may be subjected to medical, scientific or other experiments without his or her free consent". This provision in terms of clinical trials is detailed in the Article 43 of the Federal Law "On Circulation of Medicines" [6] that focuses on the fundamental rights of research participants. These include:

- voluntary participation in clinical trials;
- awareness of subjects or their legal representatives of significant trial aspects: drug safety, purpose and duration of trials, compulsory life and health insurance, guarantees of confidential participation in clinical trials
- the right to withdraw from trials at any stage;
- prohibition of vulnerable groups from participating in clinical trials: children, pregnant and lactating women, except for trials of drugs intended exclusively for these groups;
- a special procedure for the participation of military personnel in clinical trials: possible only in trials of drugs developed for the use during military operations and emergencies;
- a special procedure for the participation of persons with mental disorders and those recognized as legally incompetent: it is possible only in trials of drugs for the treatment of mental disorders and with the permission of legal representatives;
- absolute prohibition for orphaned children/children without parental care, law enforcement officers, individuals serving sentences at places of confinement, or individuals in custody at detention facilities.

In addition to providing subjects with these rights, the government assumes responsibility for safety and ethical compliance in clinical trials. The fulfillment of this obligation is ensured by two statutory provisions: the authorization procedure for conducting clinical trials and specific requirements for healthcare institutions offering facilities for such trials.

Focus on each of these regulatory provisions in more detail. The authorization procedure is an administrative step when the Russian Ministry of Health verifies the completeness of filed documents, then sends the file for two parallel examinations: an ethical review (conducted by the Ethics Committee) and review of documents prior to issuing an authorization for clinical trials (conducted by the Scientific Center for Expert Evaluation of Medical Products of the Russian Ministry of Health (Federal State Budget Institution). If both examina-

[6] Federal Law No 61 FZ "On Circulation of Medicines" from 12.04.2010 (amended on 12.04.2016) // Law reference system "Consultant- Plus"

tions are positive, then the Ministry of Health of Russia decides whether it is possible to issue an authorization for clinical trials[7].

It is the Ethics Committee that ensures the respect of rights and freedoms of subjects in the process of clinical trials. We wholeheartedly agree with B. G. Yudin, according to whom "the key purpose of the ethical review is to determine the risk for subjects related to their participation in clinical trials and whether this risk is justified by the importance of new scientific insights to be obtained in the course of such trials. Thus, it is about one of the mechanisms helping to protect participants in trials[8]. "It is worth noting that the today's Russia has a two-level system of ethical control: 1) The Ethics Board under the Ministry of Health of the Russian Federation whose scope includes an ethical examination of clinical trial documents, 2) Local ethics committees created "at healthcare, research and educational medical institutions and designed to ensure compliance with the ethical standards and protect interests of participants in drug clinical trials"[9].

The specific nature of the "ethical review" system stipulates the statutory consolidation of the main principles of the Ethics Committee's activity through "independence, transparency, justice, respect of human and civil rights and freedoms, the rights of legal entities, lack of bias, competence, expert responsibility for the procedure and quality of ethical review" [10].

Notwithstanding the problem didn't disappeared and the actual state of things fails to meet expectations. According to the findings of the Federal Service for Surveillance in Healthcare (Roszdravnadzor), "both researchers and committee members perceive the procedure as a pure formality, with all that it entails. One example is illustrative: the inspection of one of healthcare organizations revealed that the ethics committee established at the organization was almost entirely composed of this institution's senior leaders, some of whom were actively involved in clinical trials.

The only independent member of the committee in the list was an priest, however, Roszdravnadzor failed to evidence his participation in the meetings and, generally, his contribution to this ethical committee"[11].

The generalized statistical data contained in the article written by E. V. Kosenko, E. S. Rogova demonstrate poor compliance with ethical requirements in clinical trials. According to Roszdravnadzor, 15% of total violations of the clinical practice in research centers in 2015 were those in the operation of local ethics committees (moreover, such committees

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[7] Order of the Minzdravsotsrazvitiya of Russia "On the procedure for granting permits for the clinical trial" No 748n from 26.08.2010 (amended on 13.03.2015) // Law reference system "Consultant- Plus"

[8] Yudin B.G. From ethical to humanitarian expertise. M.: Sence. 2006.

[9] Term of reference for local ethics committees (REK) FGBOU VO KGMU the Ministry of Health of the Russian Federation [Electronic resource]. – URL: http://www.kurskmed.com/nauka_region_et_com/uploads/a5c7849.pdf

[10] Order of the Ministry of Health of the Russian Federation No 986n from 29.11.2012 "On the procedure of Ethics Committee"// Law reference system "Consultant- Plus"

[11] Kosenko V.V., Rogov E.S. Government control of clinical trials: experience of audit // Vestnik of Roszdravnadzor. 2015. № 2. P. 13-18.

were not established at all audited institutions). About one half of these violations (44%) are connected with the non-compliance with the statutory acts regulating their activities, 23% are connected with violations of the regulatory requirements, whose compliance is monitored by these organizations themselves. In 13% of cases, the committees ignored requests to assess the qualifications and experience of their researcher. The authors also describe such egregious violations when committees ignored conflicts of interests, did not follow up trials or estimate the amount of financial compensation for subjects, etc[12].

The above mentioned facts testify the negligence of local committees in meeting the requirements aimed, first of all, at protecting health rights of subjects, which in turn casts a shadow on the effectiveness of the existing local ethical control.

The second statutory provision focused on the state's responsibility of ensuring the safety of clinical trials was reflected in special requirements for healthcare institutions that offer facilities for such trials.

According to paragraph 7 Art. 38 of the Federal Law "On circulation of medicines", "clinical trials can be conducted only in respectively accredited healthcare facilities"[13]. The accreditation of such healthcare facilities refers to the scope of the Russian Ministry of Health and is based on the requirements contained in the Order of the Government of the Russian Federation No. 683 of 03/09/2010 "Approval of Accreditation Rules for Healthcare Organizations to Conduct Clinical Trials of Medicines"[14]. According to the reference legal system Garant, 1,185 healthcare institutions were accredited as of 2016[15].

The relationships between a pharmaceutical company and a healthcare organization conducting trials are documented in a contract governing drug clinical trials. This type of contract is regulated just by the only Article 41 of the Federal Law "On circulation of medicines" that reflects only the material contract terms and contract parties.

Such poor regulation of a seemingly insignificant issue raised a serious problem threatening the independence of researchers from sponsors, and, consequently, safety of trial participants.

Currently, there are two models of contractual relations used: "one-level" and "two-level". The first one is characterized by traditional parties: a drug developer (a pharmaceutical company) and a healthcare organization.

The second model, in turn, is complicated by an additional contract concluded with the principal researcher as an individual, which, under the Civil Code of the Russian Federa-

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[12] Kosenko V.V., Rogov E.S. Government control of clinical trials: experience of audit // Vestnik of Roszdravnadzor. 2015. № 2. P. 13-18.

[13] Federal Law No 61 FZ "On Circulation of Medicines" from 12.04.2010 (amended on 12.04.2016) // Law reference system "Consultant- Plus"

[14] Order of the Government of the Russian Federation No. 683 from 03.09.2010 "Approval of Accreditation Rules for Healthcare Organizations to Conduct Clinical Trials of Medicines" (amended on 04.09.2012) // Law reference system "Consultant- Plus"

[15] The list of health centers accredited for the clinical trials // Law reference system "Garant"

tion[16], is correctly named a fee-based service contract. And, since a separate law does not contain a ban on this kind of contractual arrangement, it is the default presumption "what is not allowed, is forbidden", as well as the freedom-of-contract doctrine that enable the existence of a "two-level" model of contractual relations.

The point of view from which we approach prescribes that "two-level model" demonstrates a number of contradictions that are incompatible with the fundamental principles of clinical trials. First, the legal grounds for a civil law contract with the principal researcher are unclear, since a special statutory requirement for a healthcare organization is accreditation; there is no accreditation for individuals. Moreover, a party as an individual must have a license to carry out medical activities; after all, he/she is actually engaged in sole practice. Second, as E. I. Matsenko points out, "there is a problem of "dual payment" for the researcher's work.... A healthcare organization as an employer must remunerate an employee.... Still, the company under a direct contract with the researcher also remunerates the latter for the same work"[17]. Third, there is a risk of a researcher's self-interest provoked by high payment rates for effectiveness.

Obviously, it is impossible to dogmatize about the opportunistic nature of the "two-level" model of contractual relations, but in conclusion, we would like to quote an article published in Moskovsky Komsomolets newspaper immediately after the notorious corruption scandal in St. Petersburg hospitals: "The area of clinical trials is delicate both from the legal and ethical viewpoint. A medical researcher paid by a pharmaceutical company has an obvious commercial interest and is unlikely to think about interests of patients and drug safety"[18].

Another practical mechanism aimed to ensure the rights of subjects that stands not just for the safety of clinical trials, but also for the economic protection of patients' interests, is compulsory life and health insurance. According to the Article 44 of the above law, the institution which has obtained a permit for a drug clinical trial shall insure the life and health of patients involved in drug clinical trials at its own expense as an insurant by making a contract for compulsory insurance". The detailed regulation of insurance issues is contained in the Order of the Government N 714 "On approval of standard rules for compulsory life and health insurance of patients participating in clinical trials"[19]. This document, in addition to general information about the insurable interest, risk insured and the amount of coverage, specifies the need to assign an individual ID code to each patient enabling to keep personal records of subjects and yet maintain proper confidentiality.

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[16] Civil Code of the Russian Federation No 51 FZ from 30.09.1994 (amended on 28.03.2017) // Law reference system "Consultant- Plus"

[17] Matsenko E. I. Legal problems of contract regulation clinical trials // The journal of law and economic research// 2013. № 4. P. 109-115.

[18] Molchanova I. Sweet medicine// Moskovsky Komsomolets. 2013. № 26160. P. 5.

[19] Order of the Government No 714 from 13.09.2010 "On approval of standard rules for compulsory life and health insurance of patients participating in clinical trials" (amended on 15.10.2014) // Law reference system "Consultant- Plus"

Despite the apparent potential of the insurance system, there are many concerns about the real efficacy of this way of protecting the rights of subjects. In the article focused on the litigations connected with the participation of patients in clinical trials, E. I. Matsenko[20] concludes about the declarative nature of the mechanism of compulsory insurance of subjects in terms of compensation for the harm caused to their health. The author notes that "there are almost no legal claims directly from patients that participated in clinical trials"[21]. We found a number of such court decisions: the appellate ruling of Moscow District Court of Ryazan No. 2-1095/2015[22], the decision of Leninsky District Court of Tambov No. 2-865/2016[23], in both cases the court directed the verdict not in favor of the applicants who tried to claim insurance indemnification, since the forensic medical examination established the lack of a cause-and-effect link between taking medications and deteriorating health of the subjects. Nevertheless, there also exist some precedents when insurance companies compensated for the harm caused to the health of subjects in clinical trials: the appellate ruling of Sverdlovsk Regional Court No. 33-10810/2016[24], the decision of Zamoskvoretsky District Court of Moscow No. 2-4648/2014[25]. A stepwise change in the existing legal practice that occurred in follow-up of the article published by E. I. Matsenko "Legal aspects of contractual regulation of drug clinical trials", testifies the growing experience in resolving disputes related to the recovery of insurance claims for harm caused by the participation in drug clinical trials.

It is worth noting that lawsuits filed by relatives to the insurer in the case of death, are generally satisfied by courts, provided there is a cause-and-effect link between these events. The examples here are the appellate ruling of Samara Regional Court No. 33-3130/2016[26], the decision of Bezenchuk District Court No. 2-322/2015[27], the appellate ruling of St. Petersburg City Court No. 33-16282/2014[28]. (Note: courts satisfy claims only if there is a forensic report on the cause of death; if such document is unavailable, the causal link between taking an experimental drug and death is not obvious for the court and may result in claim dismissal. The decisions of Oktyabrsky District Court in Murmansk No. M-363/2014[29], Tselinny District Court of the Republic of Kalmykia No. M-113/2014[30], Oktyabrsky District Court of Arkhangelsk No, 2-8081 / 2016[31] are illustrative here.

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[20] Matsenko E. I. Legal problems of contract regulation clinical trials // The journal of law and economic research// 2013. № 4. P. 109-115.
[21] The appellate ruling of Moscow District Court of Ryazan No. 2-1095/2015
[22] The decision of Leninsky District Court of Tambov No. 2-865/2016
[23] The appellate ruling of Sverdlovsk Regional Court No. 33-10810/2016
[24] The decision of Zamoskvoretsky District Court of Moscow No. 2-4648/2014
[25] Matsenko E. I. Legal problems of contract regulation clinical trials // The journal of law and economic research// 2013. № 4. P. 109-115.
[26] The appellate ruling of Samara Regional Court No. 33-3130/2016
[27] The decision of Bezenchuk District Court No. 2-322/2015
[28] The appellate ruling of St. Petersburg City Court No. 33-16282/2014
[29] The decisions of Oktyabrsky District Court in Murmansk No. M-363/2014
[30] The decisions of Tselinny District Court of the Republic of Kalmykia No. M-113/2014
[31] The decisions of Oktyabrsky District Court of Arkhangelsk No. 2-8081 / 2016

It seems that such a paradox is due to the lack of a mechanism for the subsequent health monitoring of subjects. Still, all guidance materials for medical researchers state about the risk of late side effects. The above factor, according to the E. I. Matsenko article, is aggravated by "the insufficient legal literacy when patients fail to link the deterioration of their health with the participation in clinical trials, as a result, they do not appeal to insurance companies and courts"[32].

All the above mentioned facts help us to fully share the author's concerns about the "latent nature of harm caused to the health of patients participating in clinical trials".

We presume that the cause of the problem lies in the area of statutory regulation, since, first, there is no administrative control and monitoring of adverse health effects, as well as deaths, and second, there is no formalized obligation for an autopsy in the event of a clinical trial participant's death both during the period of trials or within three years afterwards (the official period of claim application under the insurance policy). It is also proposed to introduce by-laws that would clarify issues related to the establishment of a cause-and-effect link between a patient's participation in clinical trials and health deterioration or death. In the above mentioned article, E. I. Matsenko advises "that it is preferable to provide additional control by delegating powers to Roszdravnadzor to carry out inspections if there is a link between the effect of a drug on the human body after clinical trials both at the stage of the applicant's appeal to the insurer and at the stage of the court proceedings"[33].

The next type of biomedical research reflected in the laws of the Russian Federation is clinical testing. This type of healthcare was spurred by the updated state policy in public health postulating translational medicine as the bedrock for an effective healthcare system. It is worth mentioning that the short-term existence of this type of biomedical research, and, consequently, the lack of legal practice, as well as scientific literature resulted in a simplified nature of assumptions.

The legal consolidation of the chosen development area was soon underway, the alignment of theoretical and legal frameworks took place in 2015 with the amendments to the Federal Law "On the Fundamentals of Health Care in the Russian Federation" introducing a new type of medical care – clinical testing.

Clinical testing is a practical application of developed and previously unused methods of prevention, screening, treatment and rehabilitation to confirm their effectiveness[34].

The basis for the clinical testing of the developed method is, first, the opinion of the Ethics Committee of the Russian Ministry of Health, and second, the approval of the Expert Council of the Ministry of Health.

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[32] Matsenko E. I. Legal problems of contract regulation clinical trials // The journal of law and economic research// 2013. № 4. P. 109-115.

[33] Matsenko E. I. Legal problems of contract regulation clinical trials // The journal of law and economic research// 2013. № 4. P. 109-115.

[34] Federal Law No 323 FZ "Act of public healthcare" from 21.11.2010 (amended on 12.04.2017) // Law reference system "Consultant- Plus"

This type of biomedical research is characterized by means of protecting patients similar to the previous ones, namely: the authorization procedure and special requirements for healthcare institutions offering their facilities for clinical trials.

The Ethics Committee issues an opinion on the ethical justification of using the method of prevention, screening, treatment and rehabilitation indicated in the file of clinical testing, and also agrees the report of clinical testing.

The function of the expert council is to authorize the provision of healthcare services by way of clinical testing that includes: determining the number of patients to be provided with medical care by way of clinical testing; determining healthcare organizations involved in providing healthcare by way of clinical testing on the basis of eligibility criteria established by the Government of the Russian Federation, as well as assessing the financial costs of providing healthcare for each clinical testing report and other functions stipulated in the statute of the expert council.

According to V. I. Starodubov, F. N. Kadyrov, V. I. Perkhov, O. V. Obukhova, "under the applicable laws, the development of a clinical testing report, as well as medical care by way of clinical testing, is the exclusive domain of federal medical organizations (hereinafter referred to as FMOs)"[35]. The expert council meets to decide on the compliance/non-compliance of a federal medical organization with the eligibility criteria. These include: bed capacity, sufficient medical staff, the share of healthcare professionals with academic credentials, the Hirsch index of the organization, the experience of interaction with foreign academic and medical organizations, etc.

Candidates for clinical testing are selected among patients forwarded to the federal medical organization for medical care. The decision on the appropriateness of a patient's participation in clinical testing is made by the medical commission. Clinical testing is possible only after a patient gives a voluntary consent for the provision of medical care by way of clinical testing.

However, children, pregnant and lactating women, military personnel and patients with mental disorders belong to a separate category of patients for prevention, screening, treatment and rehabilitation. Detained, imprisoned, arrested persons are prohibited to take part in clinical testing.

After clinical testing, an FMO compiles a clinical testing report and submits it to the RF Ministry of Health and the Expert Council with the assessment of clinical efficacy and cost-effectiveness of the tested method of prevention, screening, treatment or rehabilitation. The final decision on the efficacy/ lack of efficacy in clinical testing is taken by the Expert Council.

Clinical testing is subsidized from the federal budget under the government's program for federal medical organizations.

[35] Starodubov V. I., Kadyrov F. N., Perkhov V. I., Obukhova O. V. Clinical testing as a type of healthcare // Manager of public health.2015. № 9. P. 60-68.

Having reviewed the laws governing the procedure of clinical testing, we have identified gaps and flaws in the existing regulation:

1. Lack of priority areas for the development of clinical testing reports according to ICD codes;
2. Impossibility of quality audit;
3. Weak mechanism of state and departmental control over the procedure of clinical testing;
4. Lack of external metrics for clinical and economic effectiveness of tested method of prevention, screening, treatment or rehabilitation;
5. Poor regulation of responsibility for the harm caused to patient's life and health during clinical testing;
6. Unclear issue of payment for the patient's participation in clinical testing.

No doubt, the emergence of clinical testing will help to introduce innovations at healthcare organizations in order to enhance technologies and quality of medical care provided to patients. Nevertheless, the existing statutory provisions governing medical care by way of clinical testing requires substantial improvement of issues related to conflict of interest and derogation of human rights in the biomedical area.

To sum up we can stand that the applicable regulatory and law enforcement legislation in the Russian Federation relating to biomedical research is far from perfect, and, consequently, fails to ensure the proper protection of human life and health.