REAL-WORLD DATA IN LEGAL FRAMEWORK OF THE RUSSIAN FEDERATION

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The real-world data (RWD) constitute a modern trend in the healthcare system and in the structure of taking decisions. The trend is being actively developed in the Russian Federation. Ethical aspects of these trials and legal regulation of RWD are, however, still unresolved. In this paper, development of the legal field and national regulation of RWD in Russia is discussed during registration, assessment of healthcare technologies, management of patient registries, and development of clinical recommendations. It is shown that the acting regulatory field of the Russian Federation contains no bans on the use of RWD to support regulatory decisions. Nevertheless, the existing legal laws set limited opportunities for practical application and accounting of RWD by the competent authority. In conclusion, recommendations on further development of RWD legal field in Russia are provided.

Key words: real-world data, regulatory framework

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ДАННЫЕ РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ: ПРАВОВОЕ ПОЛЕ В РФ

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Данные реальной клинической практики (РКП) — современный международный тренд в системе здравоохранения и в структуре принятия решений. Данное направление активно развивается в Российской Федерации. Однако остаются не решенными этические вопросы проведения данных исследований и правовое регулирование РКП. В статье обсуждаются развитие правового поля национальное регулирование РКП в России: при регистрации, оценке технологий здравоохранения, при введении регистров пациентов, формирование клинических рекомендаций. Показано, что в действующем нормативно-правовом поле Российской Федерации нет прямых запретов на использование данных РКП для поддержки принятия регуляторных решений. Тем не менее, существующие нормы права предусматривают ограниченные возможности для практического применения и учета данных РКП со стороны уполномоченных органов власти. В заключении, даны рекомендации по дальнейшему развитию правового поля РКП в России.

Ключевые слова: данные реальной клинической практики, правовое регулирование

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In the recent years, there has been an active public discussion of the modern healthcare system and its place in decision making structure such as real-world data (RWD) and real-world evidence (RWE) [1]. In 2022, Decision of the Council of the Eurasian Economic Commission No. 78 'On introduction of changes into the Rules of registration and expertise of human medicinal products' contains definitions of real-world data (RWD), which relate to a patient's health and/or aid provision and are obtained from different sources. Evidence obtained during analysis of real-world data represent clinical evidence in relation to the use and potential benefit or risk of using a medicine obtained when real-world data were collected and analyzed [2]. Main sources of RWD include electronic health record (EHR) databases and integrated EHR; registries; insurance fund data; patient reported outcomes; outcomes of trials, mainly observational trials, etc. [3–6]. At the same time, ethical issues raised during these trials and regulatory framework of RWD remain globally unsolved.

REGULATION IN THE RUSSIAN FEDERATION

It is shown that the acting regulatory field of the Russian Federation contains no bans on the use of RWD to support regulatory decisions. Nevertheless, the existing legal laws set limited opportunities for practical application and accounting of RWD by the competent authority.

REAL WORLD DATA AND ISSUES OF STATE REGISTRATION OF MEDICINES WITH THE NATIONAL PROCEDURE

In spite of transition of the Russian Federation to registration of medicines as per the rules of the Eurasian Economic Union since January 1, 2021, marketing authorizations issued in accordance with Federal Law as of April 12, 2010 No. 61-FZ 'On circulation of medicines' (hereinafter referred to as Law No. 61-FZ) (which, however, should correspond to the legislation

of the Eurasian Economic Union) are still valid in Russia until December 31, 2025; national registration of separate categories of medicines is still possible within Government Decree of Russia as of April 3, 2020 No. 441 'On peculiarities of circulation of medicines for human use in the face of the threat, occurrence and elimination of an emergency situation, and provision medical aid to persons suffered in the result of emergencies, prevention of emergencies, prevention and treatment of diseases, which constitute a danger to the public, diseases and disorders obtained due to unfavorable chemical, biological and radiation factors' (hereinafter referred to as Decree 441); and Government Decree of Russia as of April 5, 2022 No. 593 'On peculiarities of circulation of human medicinal products in case of a defect or risk of a defect of medicines due to economic restrictions imposed on the Russian Federation' (hereinafter referred to as Decree 593).

Law No. 61-FZ, Decree 441 and Decree 593 contain no terms 'real-world data' or 'real-world evidence', or specialized standards in relation to collection, analysis and use of respective data and evidence. However, Decrees 441 and 593 establish the possibility of accelerated national registration of medicines intended for use in case of emergencies or medicines with a found defect (risk of defect) if the applicant agrees to follow postmarketing measures. The measures can include reported side effects, adverse reactions, serious adverse and unexpected adverse reactions, drug interactions, individual intolerance, other facts and circumstances, which threaten human life or health, or influence the change in the ratio between the expected benefit and possible risk of use of the medicine, detected at all stages of circulation, submitted to the Federal Service for Surveillance in Healthcare, including with the use of web-sites and mobile apps.

Thus, both Decree 441, and Decree 593 indirectly allow using RWD and related RWE as part of compliance with postmarketing surveillance measures by the applicant. It can, however, be used not independently but as part of acting common procedures established by the law. It should also be noted that decision about the possible accelerated state registration of a drug in case of emergency or defect is taken based upon agreement with a commission of experts and (or) ethics council.

RWD AND ASSESSMENT OF HEALTH TECHNOLOGIES

Russian experts repeatedly noted the prospects of using RWD to assess health technologies and compile a list of medicines (such as Essential Drug List), etc. However, irrespective of related offers developed by a professional community and additions to Law No. 61-FZ and Government Decree of Russia as of August 28, 2014 No. 871 'On approval of the Rules for the formation of lists of medicines for human use and minimal assortment of medicines required to render medical aid', direct standards on the possible use of RWD and related RWE have not been included into the legal field yet. According to experts, however, the RWD have been used by pharmacoeconomists de facto for many years to perform clinical and economic analysis and effect on the budget.

Indirect accounting of RWD is set in subpar. (c), par. 5 of the Rules for the formation of a list of medicines, which are purchased in accordance with their trade names (hereinafter referred to as the List) approved by Decree of Government of Russia as of November 28, 2013 No. 1086. In accordance with it, the possible inclusion/exclusion of medicines into/from the List is reviewed based on the outcomes of pharmacovigilance, including data on effectiveness and safety when medicines of different trade names are replaced within the same international non-proprietary name.

At the level of legislation, however, there are examples of successful formation of regional preferential lists of medicines, including the ones taking into account RWD. Thus, in particular, Moscow Government Decree as of December 24, 2021 No. 2180-ПП 'On organization in Moscow of the observational study of effectiveness of some medicines to treat oncological diseases' (along with the 'Order of organization of the observational study of effectiveness of some medicines to treat oncological diseases') shows that citizens with oncological diseases who voluntarily participate in the observational study organized in Moscow obtain compensation for acquisition of administered medicines until December 31, 2023. The observational trial outcomes are examined by 'Moscow Oncological Society' Regional Public Organization to make up suggestions for inclusion of medicines into the system of preferential provision of medicines in Moscow. Respective regional experience can be upscaled in other Russian regions, including the perspective of ethical aspects and better affordability of medical aid.

APPROACHES TO COLLECTION AND USE OF HEALTH-RELATED DATA GENERATED BY MEDICAL DEVICES AND MOBILE APPS

The possibility of distant surveillance over a patient's health using medical devices intended to monitor the state of the body is set in Federal Law as of July 29, 2017 No. 242-FZ 'On introduction of changes into separate legislative acts of the Russian Federation regarding the use of information technologies associated with health protection'. Meanwhile, as per the order of organization and provision of medical aid with the use of telehealth technologies approved by Law of the Ministry of Health of Russia as of November 30, 2017 No. 965н, data can be registered in an automatic mode while using medical devices that can transfer data. The legislation, however, regulates only a small segment of actual doctor-patient relationships. It is reduced to control of patient's health-related values and emergency response when health-related values are deviated from limits. Collection, analysis, generalization and subsequent use of respective data are not regulated by a comprehensive acting legislation.

Nevertheless, on December 9, 2022, Government Decree of Russia No. 2276 'On establishment of experimental legal regime in the sphere of digital innovations and approval of the Program of experimental legal regime in the sphere of digital innovations in a medical activity with the use of collection technologies and treatment of health-related data and diagnoses of citizens regarding the implementation of the initiative of social and economic development of Russia entitled 'Personal medical advisors' was adopted. On December 28, 2022, Government Decree of Russia No. 2469 'On implementation of the pilot project related to remote surveillance over a patient's health using the 'Personal medical advisors' information system (platform)' was adopted. As per the documents, a pilot project regarding remote surveillance over health of patients with arterial hypertension and diabetes mellitus is planned to be implemented until December 31, 2024. Treating physicians can use the data to control vital signs (blood pressure, heart rate, glycemia, at the first stage), which will be recorded by medical devices with the function of remote data transfer. The data are assumed to be transferred to the information system in an impersonal form. Data can be analyzed and treated with the help of AI technologies.

RWD AND PATIENT REGISTRIES

Federal Law as of November 21, 2011 No. 323-FZ 'On fundamentals of health protection of citizens of the Russian Federation' (hereinafter referred to as Law No. 323-FZ) provides for the creation and management of federal registries of patients with separate nosological groups such as Federal registry of HIV-infected persons, Federal registry of persons with TB, Federal registry of persons with life-threatening and chronic progressive rare (orphan) diseases that reduce the life of citizens and incapacitate them; Federal registry of persons with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant tumors of lymphoid, blood-forming and related tissues, disseminated sclerosis, haemolytic uremic syndrome, systemic-onset juvenile arthritis, types I, II and VI mucopolysaccharidosis, unspecified aplastic anemia, hereditary deficiency of factor II (fibrinogen), VII (labile), X (Stuart-Power) and in persons following transplantation of organs and (or) tissues. Law No. 323-FZ also provides for creation and management of the Federal registry of citizens who are eligible for provision of medicines, medical devices and specialized medical foods at the expense of budgetary allocations from the federal budget and budgets of the regions of the Russian Federation.

Every respective registry is managed in accordance with a special act of Government of the Russian Federation. Moreover, comparison of the registry sections shows that an emphasis is made on the formal collection and analysis of data, subject to the planning of the need in and calculation of the scope of budgetary means to provide patients with medicines, but not on collection, analysis and wide use of real-world clinical data.

Meanwhile, respective registries are managed by the Ministry of Health of Russia and authorized bodies of constituent entities of the Russian Federation, which have to ensure confidentiality of data contained in the federal and regional segment of respective registries, storage and protection of these data in accordance with Federal Law as of July 27, 2006 No. 152-FZ 'On personal data' (hereinafter referred to as Law No. 152-FZ). So, the acting regulations of the Russian Federation state that federal registries can be widely used to analyze real-world data in spite of significant potential use of a respective tool.

As far as ethics and protection of personal data go, the possibility to refer to the federal registries requires significant analysis and elaboration to protect data and basic legal values of patients.

RWD AND ESTABLISHING CLINICAL RECOMMENDATIONS

Compulsory development and review of clinical recommendations are set in Federal Law as of December 25, 2018 No. 489-FZ 'On introduction of changes into article 40 of Federal Law 'On compulsory medical insurance in the Russian Federation' and Federal Law 'On fundamental healthcare principles in the Russian Federation' regarding clinical recommendations. Meanwhile, in accordance with Order of the Ministry of Health of Russia as of February 28, 2019 No. 103н 'On approval of the manner and time of development of clinical recommendations, their review, typical form of clinical recommendations and requirements for their structure, composition and scientific validation of data included into clinical recommendations' (hereinafter referred to as the Order of development and review of CR), clinical recommendations are reviewed at least once every 3 years and no more than once every 6 months.

As per the Order of CR development and review, working groups are formed to develop and review clinical recommendations by medical professional non-commercial organizations. Working groups can include specialists who take part in rendering medical aid in case of a disease or condition (group of diseases or conditions), which demand development of clinical recommendations, scientists, specialists in evidence-based medicine, social workers, representatives of patient organizations, lawyers, representatives of insurance medical organizations, specialists in information technologies and international consultants.

The acting regulations do not exclude the possibility to use the RWD when clinical recommendations are developed if the data are presented and reviewed by respective working groups. Meanwhile, the Order of CR development and review contains generalized methodological approaches to assessment of body of evidence, which make it possible to record RWD when clinical recommendations are formed, and specialized scales assessing the levels of evidence, prevention, treatment and rehabilitation, in particular. However, experts developing clinical recommendations note that it can be complicated to use the mechanisms to assess RWD in practice.

It is also essential to take into account ethical aspects of using RWD when clinical recommendations are formed, especially while mentioning such a young Russian institution as off-label drugs (see part 14.1 of article 37 of Law No. 323-FZ).

EXPERIMENTAL LEGAL REGIME AS A LEGAL BASIS TO COLLECT RWD

RWD collection and analysis require flexible legal regulation, whereas provision of access to medical data and treatment of medical information are significantly complicated by the presence of rigid legal structures, including requirements for protection of personal data and patient confidentiality. To get rid of excessive administrative barriers in the Russian Federation, Federal Law as of July 31, 2020 No. 258-FZ 'On experimental legal regime in the sphere of digital innovations in the Russian Federation' was adopted. It created a legal basis to exempt certain innovative projects from the impact of restrictive legal standards and implement the projects within the so-called 'regulatory sandboxes'.

Moreover, Federal Law as of July 2, 2021 No. 331-FZ 'On introduction of changes into separate legislative acts of the Russian Federation due to the adoption of Federal Law 'On experimental legal regime in the area of digital innovations in the Russian Federation' created a legal basis for non-use of some rigid requirements (regarding treatment of personal data, regarding the possibility of rendering medical aid with telehealth technologies, etc.) for the subjects of the experimental legal regime.

Thus, an economic entity with a status of an operator of an experimental legal regime can obtain additional possibilities to collect and treat anonymized RWD obtained from medical cards of patients.

DISCUSSION OF OBTAINED DATA AND RECOMMENDATIONS

Use of RWD can be an essential tool for regulating authorities while assessing safety and effectiveness of medicines.

Analysis of RWD can provide an idea that a medicine can influence patients in a real life, and not under controlled clinical trials only. This will enable to detect side effects and other factors. which can influence safety and effectiveness. In this

regard, RWD can expand our idea of effectiveness and safety of a medicine.

RWD can also be used for continuous monitoring of medicines after their release to the market. This allows us to identify rare or long-term side effects, which can't be manifested in initial studies, especially if enrollment of patients from different population groups and patients with aggravated history and comorbid conditions was not possible due to objective reasons. Moreover, RWD analysis can also help develop more individualized approaches to treatment taking into account diversity of patients and their needs.

However, there exist some challenges associated with the use of the data, including the need in patient's confidentiality, and potential data distortion due to non-representativeness of the sample. So, approaches to collection and analysis of RWD and especially while taking regulatory decisions should be improved.

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