DEAR COLLEAGUES,

On the 19th of September 2024, the Association of Specialists in the Field of Health Technology Assessment, Association of Clinical Pharmacologists of the Russian Federation, and St. Petersburg Branch of the International Society for Pharmacoeconomics organized and held the V annual scientific and practical conference with international participation "RWD/RWE. Possible and Real". The topic of the conference brought together leading specialists in the field of RWD/RWE.

During the Plenary Session, the following distinguished speakers addressed the conference participants with welcoming remarks: Academician V. I. Petrov, Chief External Expert in Clinical Pharmacology of the Russian Ministry of Health; Academician A. G. Rumyantsev, Scientific Director of the Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology; S. V. Glagolev, Deputy Minister of Health of the Russian Federation; E. A. Maximkina, Director of the Federal Center for Planning and Organization of Drug Supply of the Russian Ministry of Health; A. S. Kolbin, Chairman of the Association of Health Technology Assessment Specialists; Academician A. L. Khokhlov, Rector of Yaroslavl State Medical University; R. S. Kozlov, Rector of Smolensk State Medical University, Corresponding Member of the Russian Academy of Sciences; V. V. Kukava, Executive Director of the Association of Innovative Pharmaceutical Companies; L. V. Matveeva, Executive Director of the Association of International Pharmaceutical Manufacturers. The Plenary Session was moderated by Yelena Voytsekhovskaya, Medical Journalist, Editor-in-Chief, and Author/Host of medical programs.

Across seven symposiums, leading Russian and international experts in RWD/RWE delivered presentations, including: Guvenc Kockaya (ECONiX Research & Yeditepe University); Dr. Arun Bhatt (Consultant — Clinical Research & Drug Development); M. V. Davydovskaya (Pirogov Russian National Research Medical University); M. Yu. Samsonov (R-Pharm Group of Companies); N. Z. Musina (National Association of Rare Disease Experts); D. A. Rozhdestvensky (Eurasian Economic Commission); R. R. Niyazov (Scientific Consulting Center); M. A. Borzova (Trubor Law Firm); B. V. Zingerman (National Medical Knowledge Base Association for AI Developers and Users in Medicine); A. N. Poltoratsky (N.N. Petrov National Medical Research Center of Oncology);

K. A. Kolobova (VERBA Legal); R. R. Akhtyamov (Napoleon IT); I. G. Muravyeva (Penza State University); A. M. Alasheev (Sciencefiles); E. S. Rogov; A. A. Kurylev (N. N. Petrov National Medical Research Center of Oncology); N. Shcherbakova (Western New England University); A. Yu. Yakovlev (Aston Consulting); A. S. Kolbin (I. P. Pavlov First St. Petersburg State Medical University); M. V. Zhuravleva (I. M. Sechenov First Moscow State Medical University); N. E. Zvartau (Almazov National Medical Research Centre); A. G. Solodovnikov (Statandocs); A. V. Gusev (Webiomed); M. Yu. Frolov (Volgograd State Medical University); S. K. Zyryanov (Patrice Lumumba Peoples' Friendship University of Russia); O. V. Reshetko (Saratov State Medical University); I. N. Kozhanova (Belarusian State Medical University, Minsk); I. S. Romanova (Belarusian State Medical University, Minsk); T. A. Zhiganova (Dynasty Center); T. A. Sergeeva (I. I. Mechnikov North-Western State Medical University); K. V. Orlova (N. N. Blokhin National Medical Research Center of Oncology).

The symposiums were moderated by: V. V. Ryazhenov (I. M. Sechenov First Moscow State Medical University); M. Yu. Frolov (Volgograd State Medical University); V. V. Kalinichenko (Department of Regulation of Medicines and Medical Devices, Ministry of Health of Russia); T. I. Galimov (Data Management 365); K. V. Gorelov (Federal Service for Surveillance in Healthcare, Roszdravnadzor); Y. A. Zhulev (Russian Hemophilia Society).

The V Conference featured a dedicated symposium titled "Digital Transformation in Medical Research: Possibilities of Data Science, AI and Engineering Approaches in RWE".

The conference participants discussed tools used in real-world studies, the growing importance of RWE in the modern medicine, law aspects and global perspectives in the world, Russia and the EAEU. In total, 28 reports were presented during the conference.

Here is the Conference resolution.

RESOLUTION

based on the results of the V annual scientific and practical conference with international participation "RWD/RWE. Possible and Real", that was held on September 19, 2024. The abbreviation Real-World Data (RWD) is used in the text.

The conference participants acknowledged significant progress achieved since the previous conference. Within the EAEU working group, the expert team has developed a

comprehensive series of guidelines (a roadmap) for the Eurasian Economic Union on the collection, analysis, and use of RWD. By Decision No. 155 of the EEC Board, General Principles for Developing the Regulation of Medicinal Products within the Eurasian Economic Union Regarding the Collection, Analysis, and Use of Real-World Clinical Practice Data have been adopted.

However, the state, expert society, non-profit organizations, and the industry face a number of urgent systemic issues that were brought up for discussion by the conference attendees.

I. During the conference the following limitations of incorporating RWD and RWE based on RWD were identified.

Regulation in Russia at the national level:

1. Lack of legislative provisions governing procedures for collecting and analyzing RWD, including established approaches to ensuring data quality, and guaranteeing the representativeness of final conclusions derived from the collected data.
2. Lack of established regulatory frameworks governing the integration of RWD and/or RWE derived from RWD analysis and their combined use with clinical trial results.
3. Lack of tools for comparing data on a particular product with patient's data because data sources in which the patient information is collected (or from which such information may be obtained) do not coordinate with monitoring systems.
4. There is currently no mechanism for organizations conducting scientific and research work to access de-identified data for secondary use while ensuring personal data protection.
5. Confidentiality of information remains the most pressing issue, which is controversial in the expert community; the same can be said about ethical aspects of studies.

The use of RWD and RWE in healthcare technology assessment in Russia at the national level:

1. Lack of regulatory patterns of RWD use, which limits its wide use in decision-making in the process of healthcare technology assessment.
2. According to the Rules for compiling the lists of medications and required drugs for the provision of healthcare approved by the Decree of the RF Government dated August 28, 2014 No. 871 on the rating scale of reliability and strength of evidence, the provision of RWD study results is the reason for a lower score than the score obtained without using such results.

3. Within the comprehensive assessment procedure for drug inclusion in the Vital and Essential Drugs List (VEDL) and other registers, observational study results may be submitted. These studies are essentially conducted under RWP conditions. Nevertheless, the lack of established regulatory frameworks for conducting such studies complicates data and evidence generation while undermining confidence in the obtained results.

The use of RWD and RWE in the development of clinical guidelines in Russia at the national level:

1. There is no established mechanism for taking into account the results of real-world studies in the development/updating of clinical guidelines.
2. There are no special regulations for the use of RWD stored in healthcare information systems by professional non-profit organizations in the process of development/revision of clinical guidelines.

The use of RWD and RWE to implement innovative models of drug provision in Russia at the national level:

1. No RWD paradigm in the national healthcare system, which does not allow for the implementation of value-based approach and innovative models of drug provision. At the same time, the launch of pilot projects on implementing innovative models of drug provision requires, amongst other things, the analysis of medicinal product effectiveness data to perform public procurement (e.g., for the "risk sharing" model).

When using patient-reported health and outcome data:

1. Unresolved issues in patient-reported outcome (PRO) data collection and analysis persist — data regarding health status, treatment course, and outcomes directly reported by patients, including symptoms, functional status, health-related quality of life, patient satisfaction, and treatment adherence. This leads to inadequate disease and symptom control, reduced treatment adherence, poorer patient quality of life, and decreased survival rates.
2. The undeniable benefits of studying patient-reported outcome measures (PROMs) include enhanced physician-patient and physician-physician communication; timely detection of disease progression symptoms and treatment-related adverse events; and patient involvement in clinical decision-making.

When implementing health informational systems as a RWD source in Russia at the national level:

1. The low-quality data collected by healthcare information systems of healthcare organizations, including clinical, statistical, and other data, and their incompatible format do not allow for systemic processing and use of RWD in decision-making process in the healthcare system.

2. The current regulatory framework lacks legal regulations for secure collection and analysis of de-identified healthcare data, which impedes research, development, and ultimately limits access to RWD.

3. Objectivity of published medical-statistical data and its alignment with RWD remains an unresolved issue.

4. There is no established mechanism for regulated access to RWD for healthcare providers, experts, researchers, non-governmental and commercial organizations, which would comply with personal data protection and processing legislation.

Obtaining RWD from registers in Russia at the national level:

1. The Federal Register groups data by individual categories of patients (list nosologies and persons entitled to state social assistance).

2. Lack of a uniform register of patients receiving healthcare services as part of the state healthcare system, i.e. register unifying all registers.

3. There is a need for regulatory adjustments in personal data processing and third-party access.

Protection and processing of personal data:

1. Current regulations conflate two distinct notions of "data de-identification": as an irreversible obligation of data processors upon achieving processing purposes (Article 5(7) of Federal Law No. 152-ФЗ "On Personal Data" dated July 27, 2006) and as a reversible action requiring subsequent protection of de-identified data (per Roskomnadzor's "De-identification Requirements and Methods", Order No. 996 dated September 5, 2013).

2. There is no formal definition of "personal data anonymization" or regulations for handling anonymized data, or data anonymization procedures (which should entail simpler requirements vs. de-identified data).

3. Lack of the possibility for interaction between organizations conducting scientific and clinical research, development and implementation of medicinal products, medical equipment

and medical devices with healthcare information systems and medical organizations, including in accordance with Decree of the Government of the Russian Federation No. 447 dated April 12, 2018; lack of a unified system containing real-world clinical practice data accessible for use by the organizations mentioned above.

Legal regulation at the level of the EAEU:

1. Methodological approaches for obtaining efficacy and safety data based on relevant real-world clinical practice data are in the final stages of development.
2. The following guidance documents have been prepared for discussion with competent authorities of the EAEU member states at the Eurasian Economic Commission platform: on biostatistics; on conducting non-interventional studies in real-world clinical practice settings; on ensuring quality of RWD and evidence derived from the analysis of such data for making regulatory decisions when regulating the circulation of medicinal products.
3. The guidance on general principles of data collection, analysis and application of real-world practice data is undergoing approval by the EEC.

II. The following solutions for the implementation of RWD were proposed during the conference.

Regulation in Russia at the national level requires:

1. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to Federal Law No. 61-ФЗ dated April 12, 2010 "On Circulation of Medicines" to incorporate terms adopted at the level of the Eurasian Economic Union. This initiative aims to further develop the national regulatory framework governing the collection, analysis, and use of RWD to address matters not currently regulated at the EAEU level.
2. RWD and/or evidence derived from RWD analysis should prospectively (in medium- or long-term perspective) become a valid source of scientific justification for regulatory decisions within the competence of national federal authorized bodies, while complying with the EAEU-level regulatory requirements.
3. Establishing a national registry of observational and other studies is required to serve as a public information source on RWD/RWE studies.
4. Establishing a body (committee) supervising the quality of methods and tools of RWD collection and processing.

5. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to Article 2 of Law No. 152-ФЗ to include the definition of "de-identified personal data". Possible approach: de-identified personal data are a set of structured and unstructured de-identified (including by means of anonymization and pseudonymization) large volume personal data characterized by a high variability rate, which are subject to automatic processing using computer algorithms to identify certain correlations, trends, and patterns.

6. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to Clause 2 of Article 3 of Law No. 152-ФЗ to introduce a direct exception stating that an entity, to which de-identified personal data on health status are transferred for processing within the framework of medical decision-making support systems, is not a personal data operator.

7. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to sub-clause 9.1, Clause 1, Article 6 of Law No. 152-ФЗ that there is no need for the subject's consent to the processing of their de-identified personal data for scientific and/or medical purposes related to the creation of medical decision-making support systems.

8. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to Law No. 323-ФЗ and other legislative/sublegislative acts, including provisions for harmonization with the EAEU legislation.

The use of RWD and RWE in healthcare technology assessment in Russia at the national level:

1. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to Clause 55, Article 4 of Federal Law No. 61-ФЗ dated April 12, 2010 "On Circulation of Medicines" "... analysis of information on comparative clinical efficacy and safety of the medicinal product including information based on RWD".

2. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to the Rules for Compiling Lists of Medicinal Products for Medical Use and the Minimum Range of Medicinal Products Required for Healthcare Provision, approved by the Decree of the RF Government dated August 28, 2014, No. 871 for potential use of real-world evidence in the comprehensive assessment of medicinal products.

As a baseline approach, it is proposed to incorporate RWD study designs into the evidence reliability and persuasiveness assessment scale by assigning them sufficient points to meet the threshold value (in accordance with general requirements established in the EAEU regulatory acts regarding the acquisition and use of real-world data, and subject to the establishment of positive law enforcement practice).

3. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to the Rules for Compiling Lists of Medicinal Products for Medical Use and the Minimum Range of Medicinal Products Required for Healthcare Provision, approved by the Decree of the RF Government dated August 28, 2014, No. 871 for potential inclusion into lists, provided there are agreements for risk sharing / contingent consideration concluded (with RWD and RWE collected) (according to general requirements stipulated in EAEU regulatory acts on obtaining and using RWD and provided there have been formed positive compliance practice).

4. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are to be prepared to the Rules for Compiling Lists of Medicinal Products for Medical Use and the Minimum Range of Medicinal Products Required for Healthcare Provision, approved by the Decree of the RF Government dated August 28, 2014, No. 871 for inclusion of the additional criterion "Evidence demonstrating the drug's effectiveness under real-world clinical practice conditions within the Russian Federation" to the category "additional data on the drug product" of the rating scale.

5. Industry-wide guidelines are required to ensure both the quality of RWE studies and the reliability of submitted results for comprehensive drug evaluations.

The use of RWD/RWE study results in the development of clinical guidelines in Russia at the national level:

1. In cooperation with competent executive bodies and pharmaceutical industry representatives, amendments are being prepared to Appendix 1 to the order of the Ministry of Health of Russia No. 103н dated February 28, 2019 "On Approval of the procedure and terms for the development of clinical guidelines and their revision, the model format of clinical guidelines and requirements to their structure, contents and scientific validity of the information included in the clinical guidelines" for potential wider use of RWD in the preparation of treatment guidelines and the use of such data by professional non-profit organizations for the

development/revision of clinical recommendations (according to general requirements stipulated in EAEU regulatory acts on obtaining and using RWD and provided there have been formed positive compliance practice).

The use of RWD and RWE to implement innovative models of drug provision in Russia at the national level:

1. The improvement of antimonopoly legislation aimed at ruling out the risks of unjustified use of the current norms in the innovative models of drug provision.
2. Implementing the mechanism of using RWD to assess treatment outcomes in the model of payment agreement based on treatment results (according to general requirements stipulated in EAEU regulatory acts on obtaining and using RWD and provided there have been formed positive compliance practices).

Obtaining RWD in the use of healthcare information systems in Russia at the national level:

1. Implementation of quality assurance measures for data collected/entered into healthcare information systems, including medical information systems.
2. In cooperation with competent executive bodies and pharmaceutical industry representatives, preparation and development of a set of national standards and unified regulatory reference information for medical data and record coding, aimed at ensuring compatibility and enhancing interoperability of RWD collected from healthcare information systems.
3. The establishment and use of the national register of observational and other studies, that will enable publishing information about studies and their results to ensure greater access to real-world data.

When using patient-reported health and outcome data:

1. Development of a methodology for collecting and analyzing patient-reported outcome measures (PROMs) for diseases and conditions where symptom or condition management is possible.
2. Development of mechanisms for real-time feedback on collected data.
3. Implementation of physician training programs on the use of PROMs and their effective integration into clinical practice.

When implementing information systems as a source of RWD:

1. Implementation of quality assurance measures for data collected/entered in healthcare information systems, including medical information and other systems, clinical data, healthcare service provision and payment information, other data characterizing methods and volumes of healthcare provision and payment, and statistical data.
2. Harmonization of activities among experts and expert institutions involved in developing RWD methodology and creating structured electronic medical documents and reference materials.
3. In cooperation with competent executive authorities and pharmaceutical industry representatives, addressing the regulation of third-party data access while ensuring personal data protection. One potential solution could be establishing a regulated institution of data intermediaries.

Obtaining RWD in the process of the analysis / management of registers in Russia at the national level requires:

1. The revision of approaches to the management of patient registers to improve the quality of and access to sources of reliable scientific information regarding patient population, prescribed and applied therapy, treatment results, etc.
2. The development and implementation of a uniform register for all ICD diseases including the procedures for interdepartmental interaction aimed at managing and processing data from such a register as well as potential provision of a limited access to form RWD for medical and scientific communities, commercial and non-commercial organizations.
3. Provision for obligatory use of registers in clinical practice and in the healthcare technology assessment.
4. Under the RF Government Resolution "On the Unified State Healthcare Information System", it is advisable to establish procedures for RWD collection, storage, and access; a unified RWD access system (rather than access to isolated subsystems) for healthcare providers, experts and researchers, non-governmental and commercial entities (IT sector, pharmaceutical industry, and medical/diagnostic equipment manufacturers). This requires developing a dedicated access mechanism that ensures compliance with personal data protection requirements and effective governance of personal information.

Regarding the improvement of personal data protection and processing, the following is necessary:

1. In cooperation with competent executive bodies and pharmaceutical industry representatives, preparation of amendments to Article 2 of Federal Law No. 152-ФЗ to define the terms "anonymization of personal data" and "anonymized data," distinguishing between the concepts of "anonymization" and "de-identification". Possible approach: "Anonymization of personal data" is a data processing method resulting in data aggregation that precludes association with directly or indirectly identified or identifiable individuals.; "Anonymized data" are data obtained as a result of personal data anonymization.
2. In cooperation with competent executive bodies and pharmaceutical industry representatives, preparation of amendments to paragraph 2, Article 1 of Federal Law No. 152-ФЗ to explicitly exclude the application of Federal Law No. 152-ФЗ to anonymized data. Possible approach: "This Federal Law does not apply to relations arising during the processing of anonymized data or data obtained as a result of anonymization."
3. Simplification of access to healthcare information systems for operators that are not medical or pharmaceutical organizations but are engaged in the development and supply of drug products and medical devices (equipment) or scientific and clinical research in medicine and pharmacology.
4. Expansion of the scope for processing special categories of personal data without the data subject's consent (paragraph 2, Article 10 of Federal Law No. 152-ФЗ), allowing such processing by operators that are not medical or pharmaceutical organizations but are engaged in the development and supply of medicinal products and devices (equipment) or scientific and clinical research in medicine and pharmacology for statistical, scientific, and research purposes, including processing within the operation of clinical decision support systems.

Legal regulation at the level of EAEU requires:

1. Submitting for consideration to the Working Group on Developing Common Approaches to Regulation of Medicinal Products within the Eurasian Economic Union proposals to define the concept of "RWD studies", in order to establish a clear distinction between "pivotal" registration studies and RWD studies, since their requirements and scope of application differ, as well as developing regulatory requirements for conducting RWE studies, obtaining quality data, generating evidence, and using such evidence for regulatory decision-making.

2. Submitting for consideration to the Working Group on Developing Common Approaches to Regulation of Medicinal Products within the Eurasian Economic Union proposals to standardize approaches regarding implementation of real-world clinical practice data and/or evidence derived from analysis of such data, their combined use with clinical trial results for scientific justification and appropriate regulatory decision-making.

3. Submitting for consideration to the Working Group on Developing Common Approaches to Regulation of Medicinal Products within the Eurasian Economic Union proposals on a unified approach to the collection, analysis, and use of real-world data by developing additional relevant EAEU-level guidelines concerning the use of electronic medical records as a source of real-world data; quality and transformation of real-world data; application of biostatistics principles in studies; conducting studies based on real-world data and their designs; the use of real-world data for healthcare system decision-making.

4. There is a need in facilitating accelerated adoption of international requirements as part of Good Clinical Practice by ICH GCP E6. Currently, Decision No. 79 of the EEC Council dated October 3, 2016 "On Approval of Rules of Good Clinical Practices of the Eurasian Economic Union" corresponds to ICH GCP E6 R1. Amendments corresponding to version R2 are under consideration.

5. Submitting for consideration to the Working Group on Developing Common Approaches to Regulation of Medicinal Products within the Eurasian Economic Union proposals on the need to develop special approaches regarding the use of RWD and/or evidence derived from analysis of RWD when conducting post-authorization clinical studies and/or pharmacovigilance activities. It is necessary to develop regulatory requirements for conducting and publishing non-interventional studies. For post-authorization efficacy studies (PAES) and post-authorization safety studies (PASS), compliance with "best practices" is required for the collection, management, and analysis of data with high quality and transparency levels. Monitoring of drug product effectiveness and safety should continue throughout the entire product lifecycle. PASS and PAES serve as important tools for identifying any additional risks and assessing uncertainties regarding benefit/risk profiles of drug products.

Recommendations for patient communities:

1. To be directly involved in developing recommendations for novel and efficient methods of RWE collection.

The following steps should be taken to organize interdepartmental and expert interaction:

1. Establishing working groups to address the issues mentioned above; the working groups should aim at accelerating implementation of the RWD approach and executing measures to enhance RWD use.
2. Organizing collaboration between experts and expert institutions to harmonize the RWD methodology under development; electronic medical record management approaches; and data collection and processing methods within the framework of digital transformation.

Conference presenters

September 19, 2024