Registers as the basis for data collection and evidence building

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Abstract

The development of medical science requires a constant increase in the effectiveness and safety of treatment. Collection of real-world data (RWD) is one way of solving these problems. Clinical registries are one of the most important parts of this process. Clinical registries allow collecting data on the use of medical technologies and monitoring the results of therapy in real clinical practice. The introduction of patient registers and the collection of RWD data into widespread medical practice can help optimize costs for treating high-cost diseases and to better plan the budget.

Keywords: medical registries; drug register; register of nosologies; real-world data; RWD; RWE

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Introduction

Medical registries identified by the U.S. Food and Drug Administration (FDA)as a source of real-world data (RWD) and real-world evidence (RWE), different from traditional clinical research [1].

The FDA describes **registries** as: *an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purpose. Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry)* [2].

The European Medicines Agency (EMA) describes registries as *"are organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition or exposure, and that is followed over time. Patient registries can play an important role in monitoring the safety of medicines"* [3].

Currently, we are talking about automated register systems that allow both epidemiological studies and monitoring of the clinical condition of patients at all stages of the treatment and diagnostic process, analyze the accumulated data and use them to improve the diagnosis and treatment of diseases, evaluate the effectiveness and safety of various methods of treatment, the quality of life of patients and the quality of specialized high-tech medical care, to predict the amount of its financing. Thus, patient registers are an electronic evidence database for making medical decisions [4].

It is necessary to distinguish registry. In practice, these 2 concepts are confused; practitioners, administrators, and other participants in the healthcare system, who have patient lists at their disposal, even with a wide list of data, sincerely believe that they have a medical register. When creating the register, a plan for medical and statistical analysis is not built. Therefore, it is impossible to obtain high-quality analytics that answer topical questions of real clinical practice and to collect an evidence base for making clinical decisions.

The concept of registers of compulsory medical insurance accounts has been introduced into the healthcare system. It was determined by the Federal Law of November 29, 2010, No. 326-FZ "On Compulsory Medical Insurance in the Russian Federation" [5], the general list of information is the MHI Rules approved by the order of the Ministry of Health and Social Development of Russia. The formats and an exhaustive list of transmitted data are described in the General principles for the construction and functioning of information systems and the procedure for information interaction in the field of compulsory health insurance (CHI), approved by order of the Federal CHI Fund. Account registers have a special purpose, they are a reporting tool for CHI and the basis for paying for medical care. Issues are being discussed and attempts are being made to integrate clinical registers and compulsory medical insurance registers, to migrate part of the general data, to simplify the work of a doctor and save the working time of operators of medical information systems. However, since the goals and objectives of the compulsory medical insurance and registers are different, interchangeability is impossible [6].

History of the issue in Russian and world practice

The history of medical registries goes back centuries. The first successful attempt at territorial registration of malignant neoplasms was made in 1844, when D. Rigoni-Stern published information on the incidence of skin, breast and uterine cancer among the population of Verona. The first register, approaching in structure to modern ones, can be considered the register of the Hamburg Ministry of Public Health, formed in 1929. In 1935, a regional cancer registry was organized in the United States, and in 1942 in Denmark, the first national cancer registry covering the entire population of the country. In 1950, the World Health Organization Committee on Cancer Accounting was created, which developed guidelines for creating cancer registries. By 1954, there were 18 population cancer registries in the world. In 1966, the International Association of Cancer Registries was formed. Today in the world more than 250 regional cancer registries and 100 individual oncological disease registries [7].

In Russia, the State Cancer Registry is maintained on the basis of the order of the Ministry of Health of the Russian Federation dated April 19, 1999 No. 135 "On improving the system of the state cancer registry" [8]. The purpose of creating a register of patients with malignant neoplasms (cancer register) is to obtain reliable information on morbidity, mortality from malignant neoplasms, and the state of specialized oncological care for the population. However, the rapidly developing science, laboratory diagnostics, the pharmaceutical industry, the export of medical services, the opportunity for patients to receive treatment in specialized centers located in different countries of the world, are daily correcting the established clinical practice. There is a need to analyze data from the experience of a special orientation as an adequate response to the penetration of new technologies and the emergence of new diagnostic methods and treatment programs in the arsenal of doctors. In addition to the existing cancer registry, smaller-scale, but highly demanded registries and observation programs for solving certain specific issues of practical health care are more flexible, mobile and operational solutions [9].

In Russia the first registers appeared in the 70s – 80s of the last century, and one of the first were the register of acute myocardial infarction (AMI), which was conducted under the guidance of Professor N. A. Mazur [10].

An important characteristic of registries, in contrast to clinical trials limited to clear time frames, is the duration of follow-up. A striking example is the 50-year experience of Sweden in organizing various population and health registers, which are closely interconnected and fully complement each other [11].

Since 1987, the National Register of Inpatients has been functioning, the main and concomitant diagnoses of which are coded in accordance with ICD-10, which makes it possible to objectively assess the effect of concomitant pathology on the course and outcomes. For example, in a study of the risk of developing malignant lymphoma in a cohort of patients with rheumatoid arthritis (RA) (4160 people, 9715 person-years of follow-up, 9 lymphomas) who received treatment with TNF-α antagonists, compared with a cohort of patients with early RA (3703 people, 13292 person-years of follow-up, 11 lymphomas) and a cohort of inpatients with RA (53067 people, 297102 person-years of follow-up, 319 lymphomas), no statistically significant differences were found [12].

The Swedish national register of the RA, operating since 1993, as well as the registers BARFOT (Better Anti-Rheumatic FarmacoTherapy), TIRA (Therapies in RA), STURE (Stockholm TNF-antagonist follow-up registry), SSATG (Southern Swedish antirheumatic therapies group) merge in the national ARTIS register (Anti-Rheumatic Therapies In Sweden), which has collected information on treatment since 1999, that are, since the introduction of the first biological medical product (BMP) into clinical practice in Sweden [13]. When issuing a license for treatment with these drugs, the Swedish Medical Products Agency put forward only one requirement for their use – long-term quality control of the entire treatment and diagnostic process, both at the regional and national levels. The specified registers have solved this problem. Since then, the treatment of BMP has not been administratively limited. Another task of the ARTIS registry was to prevent the indication drift for expensive therapy for rheumatic diseases. As shown by a 5-year follow-up, there was no expansion of indications for prescribing BMP according to the activity of the disease, but they began to be prescribed to patients with a lower HAQ level.

An obligatory function of the registers is to determine the risk of developing any adverse drug phenomena, but mainly delayed and potentially life-threatening (tumors, tuberculosis, AIDS, etc.). Additionally, the registers have provided rich opportunities for in-depth scientific research. Thus, in the SSTAG register, there was a statistically significant decrease in the need for surgical treatment among patients with RA who received BMP therapy [14].

The Russian Federation also has a wealth of experience in the field of rheumatology. The all-Russian register of patients with RA is maintained with the approval of the Expert Council in the field of health care of the Ministry of Health and Social Development of Russia, specializing in Rheumatology. The register was created to improve the registration of patients with RA, as well as a source of reliable information about the existing clinical practice, which makes it possible to improve the quality of medical care provided to patients. The register was created and is maintained in electronic form under the auspices of the All-Russian public organization "Association of Rheumatologists of Russia" in a long-term partnership with the company – manufacturer of registers Aston Consulting. Real-world clinical data have been

repeatedly published in Russian journals and presented at EULAR [15].

However, if we talk about the longest and widest experience of register observation in the Russian Federation, the State Register of Diabetes Mellitus, created in 1996 by order of the Ministry of Health of the Russian Federation No. 404 от 10/12/1996 epidemiological monitoring of diabetes mellitus as most important socially significant pathology [16]. In terms of the number of patients and connected users, it is the largest registry in Europe. As of 2020, there are more than 4.5 million patients in the register, hospitals from 84 constituent entities of the Russian Federation are connected [17]. Technical support and updating, medical and statistical data processing, analytical work and training of specialists from the beginning of the creation of the register providing by Aston Consulting, according to the existing legislation within the framework of public-private partnership.

Approaches to creating registers

The creation of registers and their subsequent evaluation is subject to certain rules, and strict approaches are used [18].

Registries can be prospective observational cohort studies of patients who have a specific disease and/or are receiving a specific treatment or medical intervention. The register can be retrospective, that is, use the data previously entered medical records. A combination of retrospective and prospective register types is possible. They can be used to understand the natural history of the course of the disease, assess or monitor the safety and efficacy of drugs based on randomized clinical trials (RCTs), assess the quality of care and provider performance, and assess cost-effectiveness (see Fig.) [19].

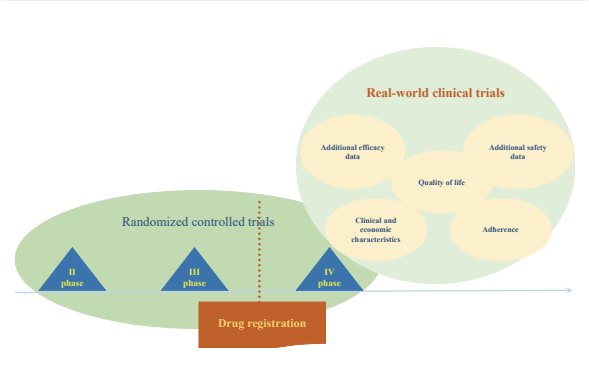

Figure. *Ratio of opportunities for randomized controlled trials and registries [19]*

The design of the register is planned in accordance with the set goals, which, in turn, predetermine the collection and analysis of the data obtained. Registries typically include a larger and more diverse patient population than those typically studied in phase III RCTs; therefore, they better reflect real-life patients, supportive services practices and treatment outcomes. Patients are followed up over a longer time, allowing long-term results to be assessed. Patients are excluded in the register randomly, but in accordance with a strict principle of consistency (that is, all patients who meet a certain criterion for a certain time). Additionally, the register can provide for long periods of observation of patients [18].

Most registry studies require few visits, assessments or procedures. The set of data for each patient must be of the same type, in addition, the inclusion of patients in the register must be continuous (that is, it must include all patients who satisfy the given register principles) and limited by the time and territorial framework specified in the design of the register. The inclusion of a patient in the registry should not be influenced by the desire or reluctance of the investigator. The data recorded in the register can be obtained both because of direct contact with the patient, physical examination, and by analyzing primary medical source. At least one data element must be key, that is, directly related to the purpose of the register [20].

Some authors classify drug registries and registries by nosological form. Drug registries aim to collect data over time from a population exposed to a study drug, or drug group, or treatment regimen. The purpose of drug registries is to study the long-term results of the use of drugs in relation to their effectiveness and safety in real clinical practice, adherence. The tasks of such a register – to collect data on adverse reactions, including using standardized patient questionnaires, to study long-term treatment outcomes, periods of remission, response to therapy, etc. [2].

Patient registries by nosological forms are a necessary tool for studying the nature and course of diseases since it is an important way to obtain a sufficient sample size necessary for research in real clinical practice. On the basis of patient registers by nosological forms, it is possible to analyze and compare long-term results of the efficacy and safety of treatment with different drugs, treatment regimens, which is more objective than drug registries [2]. Since patients (and their physicians) are not specially selected, there is a high probability that the quality of treatment and its compliance with current recommendations within the registry will vary greatly. Accordingly, there is a high probability that specific medications, even those that are mandatory in a certain clinical situation, may not be prescribed to all patients. This, in turn, makes it possible to form identical groups within the register, differing from each other by the fact of taking or not taking a particular drug [18].

Analysis of patient registers makes it possible to:

1. study the epidemiological data:
   - prevalence, morbidity, mortality, survival, distribution by stage and severity, complications;

- socio-demographic features of the disease in the regions;

2. plan the economic costs of treatment:
   - the need for diagnostics and treatment at the level of healthcare facilities, region, country;
   - health technology assessment;
3. explore differences in actual clinical practice:
   - regional features;
   - compliance of supportive services with treatment standards and clinical guidelines;
4. analyze the achievement of health targets in real time:
   - efficacy, tolerance, adherence;
   - assessment of quality of life;
5. conduct scientific analysis:
   - assessment of a representative patient population;
   - analysis of therapeutic approaches in dynamics;
   - outcomes and endpoints over a long (unlimited) period.

Legal regulation

The legal basis for operating the registers is the Federal Law dated November 21, 2011 No. 323-FZ "On the Basics of Health Protection of Citizens in the Russian Federation" [21]. Personal data protection is performed in accordance with the Federal Law on Personal Data dated July 27, 2006, No. 152-FZ [22]. Legal entities involved in the creation and operation of registers are certified operators of personal data, their activities are subject to control by Roskomnadzor of the Russian Federation. Individuals admitted to the processing of personal data in registers undergo regular training in working with personal data and ensure the confidentiality of information contained in the registers. All persons and medical organizations involved in the collection and analysis of register data, including the Ministry of Health of the Russian Federation and authorized executive bodies of the Russian Federation, must ensure the confidentiality of information contained in the register, storage and protection of such information in accordance with the Federal Law "On Personal data." The patient's personal data can be used only if he has signed an informed consent to the processing and transfer of personal data and information constituting a medical secret to the operator. The transfer of information to the register from medical organizations, physicians and specialists is conducted via a secure communication channel, in accordance with the requirements of the Federal Service for Technical and Export Control and the Federal Security Service of the Russian Federation.

Conclusion

The clinical, scientific, technical, legal and public-private partnership experience accumulated in the Russian Federation in the field of creating and maintaining registers allows us to call this source of information solid and reliable – a possible basis for studying real-world data (RWD) and real-world evidence (RWE).

ADDITIONAL INFORMATION

Conflict of interest. The author works for Aston ConsultingJSC.
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