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Modern approaches to the organization of translational research

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The growing distance between fundamental science and clinical medicine may bring risk of decreasing effectiveness of biomedical research. Translational research is a relatively new concept; it implies application of fundamental research results to practice (from bench to bedside) using a specific combination of research stages. As a result, it provides integrated information on safety, efficacy and effectiveness of a medical technology. However, there is no generally accepted view on aims and structure of translational research. This review presents analysis of different methodological approaches to translational research.
Keywords*: translational research, drugs, medical technologies.*

RELEVANCE

According to a range of experts, a disparity between the information accumulated in the course of fundamental research and practical medicine has been outlined in the setting of implementation of new medical technologies (MTs). It ought to be reminded that observers obtain the so called efficacy in the course of preclinical and clinical studies; this efficacy is specified for MT registration; doctors obtain effectiveness in the course of clinical practice [1]. The situation when data on MT efficacy do not translate into data on effectiveness is described in the foreign literature as "lost in translation" [2-4]. Several authors suggest resolving this issue radically by introducing a 10-year-long moratorium on, for instance, registration clinical studies [5]. Scientists will probably be able to assess potential of the accumulated experimental data and conduct multiple appropriate effectiveness studies in different populations, countries, regions etc. within this period. Experts distinguish between several main causes of the lost-in-translation problem [6, 7]. For instance, on the one hand, design of registration clinical studies may not conform to the actual working conditions of doctors and healthcare professionals; on the other hand, healthcare system does not always react to scientific discoveries flexibly enough. Several methodological approaches are suggested to overcome this disparity [1]. The so called route from bench to bedside is one of these approaches; it implies development of a link of interconnected fundamental and clinical studies, which are planned so that the results of each study may be compared with results of a previous study. Such continuity requires new solutions for organization, infrastructure and competence of researchers. Such polycomponent solutions, which allow translating results of fundamental research into clinical practice, are generally called translational solutions [8].
As has been mentioned before, one of the components of translational research (TR) is translation of efficacy into effectiveness. Moreover, it is necessary to ensure consistency of the

fundamental study, which sheds light onto the mechanism of action of this MT and its safety, with data of registration clinical studies. TR may also conclude with the analysis of consequences of MT introduction in the healthcare system and, when necessary, formulation of a new clinical task.

Despite the fact that the notion about TR started to develop in the end of the 1980s, there has been no common view of the issue, how translational studies ought to be performed and what is their ultimate goal [9]. This review was aimed at performing comparative analysis of approaches of different authors to methodology of translation and stages thereof.

METHODOLOGY

Articles on translational research methodology were searched in PubMed (database, www.ncbi.nlm.nih.gov/pubmed), Cochrane Reviews (www.cochrane.org) and electronic scientific library Elibrary.ru (www.elibrary.ru). The following keywords were used for the search: translational research, translatability, translational medicine. 1,294, 39 and 219 publications found for keywords "translational research", "translatability" and "translational medicine", respectively, were selected at the first stage; 1,552 articles in total. The selected publications were analyzed against the following inclusion/exclusion criteria.

Inclusion criteria: the review included the articles on general issues of translational research planning and several organizational solutions in that sphere, including assessment of potential of a translation.

Exclusion criteria: the review did not include the articles on specific translational studies in specific areas of medicine.

Thus, 33 articles were selected for this review.

Main terms
• Efficacy – effect of a medical technology produced in the conditions of registration studies [6, 7].
• Medical technologies – technologies aimed at prevention of diseases and rehabilitation of patients.
• Vaccines: drugs, medicinal proteins: medical devices (appliances); therapeutic and surgical procedures and the systems aimed at health protection and promotion [10].
• Translational (operational) research – technologies, which allow adapting results of scientific studies to clinical practice [11].
• Effectiveness – efficacy of a medical technology produced in real conditions in a specific patient [6, 7].

RESULTS

TR is primarily aimed at adapting results of scientific studies to actual conditions of clinical practice [12]. These studies imply use of a single generally accepted nomenclature, which facilitates information exchange between researchers from different countries and organizations [13].

2T concept. As has been mentioned before, TR structure remains disputable. According to the earliest model by Sung et al., translation is a two-phase process: research proper (fundamental and clinical research) and organization (practical implementation) [14, 15]. In other words, it is the route from bench to bedside (phase T1) and, subsequently, to the healthcare system in general (phase T2). It is true that scientists often define translation as application of results of *in vitro* and *in vivo* studies to a human and emphasize the most difficult for organization stage of translation from fundamental research to clinical testing [15]. New solutions in the sphere of infrastructure, training of researchers etc. are required in order to resolve this issue. E.g., some universities around the world have established programs for training researchers, who would be

familiar with specific peculiarities of both fundamental and clinical research and be able to put a link between them; a special program of the National Institutes of Health (NIH) sponsoring training of such specialists has been in effect in the United States of America since 1964 [16]. NIH provide grants (Clinical and Translational Science Awards) for organization of clinical and translational studies [12]. Training of project managers in the sphere of pharmaceutical research, who would be able to track a potential new drug from the concept to registration in the pharmaceutical market, is exceptionally interesting.

3T concept. The 3T concept (three periods of translation) was suggested in 2007 in the course of development of the so called Roadmap of medical research of the National Institutes of Health [17]. According to the Roadmap, period 1 (T1) corresponded to the translation from fundamental research data to clinical efficacy; period 2 (T2) – from efficacy to clinical effectiveness; period 3 (T3) – from effectiveness to implementation on the healthcare establishment level. The 3T concept is the most popular among scientists, although different authors interpret the stages differently. E.g., Drolet et al. modified it to be a "biomedical research translation continuum". 3T there are united into the so called translation zone, where T1 implies appraisal of applicability of the data obtained at the preclinical stage to a human, T2 – appraisal of safety and efficacy (clinical research proper), T3 – practical implementation [18]. It appears important that in such a pattern study of MT effectiveness is beyond the translation zone. Thus, effectiveness may be interpreted as the effect of real conditions of clinical practice on the drug's properties revealed at the stage of passing through the translation zone in this model.

4T concept. At the same time, Khoury et al. include the studies on results of practical implementation of a new intervention into the translation, thus outlining stage T4 [19]. This stage may involve evaluation of medical technologies and pharmacoeconomic analysis. On the other hand, Westfall et al. consider correction of clinical practice as the endpoint of translation; they see translation as a continuum, which may be continuously interrupted by validation of the data obtained at the previous stages [16].

Translational research impact on different outcomes. Spoth et al. (2013) suggested a Translational Science to Population Impact (TSci Impact) Framework: four stages of translational study functioning interconnected with back links, testing environment and the required equipment [20].

Stage 1 – pre-adoption – includes submission of an application by the researcher or the organization performing testing, accumulation of information and dissemination of information on the intervention.

Stage 2 – adoption – consists in organizational preparation, economic benefit analysis, prospective funding of the project; stimulation of the society, organizations and public officials to approve and adopt the intervention.

Stage 3 – implementation – is required for the process of analysis of means and strategies aimed at integration of the new intervention in the existing framework. This stage is characterized by analysis not only of effectiveness of this intervention among specific population groups, but also of a range of the factors predetermining its practical efficacy, such as selection and involvement of target population groups and organizations; impact on implementation quality or determination of a period, wherein this intervention will conform to its initial ends; introduction into the existing healthcare system; short-term monitoring of the intervention's effect.

Stage 4 – long-term practical use of the intervention. This stage consists in analyzing how the intervention is performed and regulated and assessing its properties, costs and support programs. All the stages depend on multiple conditions on specific tiers – national, federal, local and social – and provision of the researcher with subordinates, funding and infrastructure [20].

It is advisable to perform translational research on the basis of large-scale multicenter clinical studies with large samples. Individual studies may be translated if the obtained data are to be used by the scientists and researchers familiar with the initial results of the study. Adoption of results of such studies by clinicians, patients and public officials is undesirable, as they rarely produce data that are sufficiently adequate and elaborated to be used in clinical practice [21].

As for the fundamental preclinical research in the translational context, it must result in the information on the drug's toxicity, pharmacokinetic parameters etc. In any case, the question whether it is appropriate to extrapolate these data on the human body arises; moreover, representative models have not yet been developed for a significant number of diseases. At the same time, preclinical research helps to significantly reduce costs of the first and subsequent stages of clinical research by filtering out the fundamentally ineffective or dangerous drugs on a very early stage [22]. That is why fundamental research is an important stage of translation – it allows attaining holistic perception of an MT and avoiding failures in the futures.

Translation success prediction. After this stage is completed, it is useful for researchers to assess potential of the further translation. Thus, in 2009, Wehling suggested a scale for translation success prediction (translatability) [15]. It allows for assessment on the basis of several criteria: data of animal studies; genetic data of a person and information on disease pathogenesis; results of the previous clinical studies; description of the applied biomarkers; data of pilot studies. Each criterion is evaluated on a 5-point scale and later multiplied by a weighted coefficient adequate to the contribution of each criterion to translation success. The author emphasizes conventionality of this scale and makes a call for complex approach to the issue of translation.

Thus, preclinical stage is to be planned so as to obtain as much information about the drug as possible, which is capable of affecting further research. Results of the clinical study and the preclinical study ought to be comparable (e.g., application of adequate biomarkers) and conform to one logic. Biomarkers Consortium was founded in order to compare results. It is aimed at search and adoption of new biomarkers for intensifying competitive introduction of new technologies, drugs and approaches to prevention, early diagnosis of diseases and treatment regimens therefor [23].

One of the first times stage T1 of translational research took place was in Great Britain in the 1970s; it was dedicated to development of safe and comfortable clothes and accessories for fishers [24]. Translational research may be conducted by various organizations: pharmaceutical and biotechnological companies, universities, research institutes. However, each of these establishments focuses on one of the operational research periods. Thus, universities and other higher education providers focus on stage T1, as it allows for performing early clinical studies involving laboratories and practicing clinicians.

Scientific field "Translational bioinformatics" consists in the integration of the information received from scientists and clinicians. This program is aimed at systemizing data from various sources, drawing general conclusions concerning the performed studies and elaborating hypotheses on the basis of these conclusions. E.g., results of a person's genome analysis may be used to assess predisposition of this person to a specific diseases and predict his/her response to the standard therapy [25]. The US National Institutes of Health established the Biomedical Translational Research Information System (BTRIS). It contains the information obtained not only through clinical practice, but also by means of experiments and clinical studies, and allows planning and performing translational, prospective and retrospective studies on the basis of the available data [26].

The establishments that are focused primarily on stage T2 ought to analyze and demonstrate effectiveness of the developed treatment strategies, which appeared efficient at T1 on the population level [27]. The National Institutes of Health, similar institutions, Clinical and Translational Science Centers (CTSC) at universities and medical institutions provided NIH grants are among such establishments. E.g., Fitzgerald Center in Philadelphia (functioning under the CTSC program) launched analysis of adverse effects of the use of the selective cyclooxygenase-2 (COX2) inhibitors, which are no longer manufactured due to a proven increased risk of myocardial infarction and stroke, in 2006. Scientists are looking for the biomarkers, which will help to identify the patients, who were not affected by therapy-induced complications, in order to improve this class of drugs [28].

Translational research development. The National Center for Advancing Translational Sciences (NCATS) was established in 2011 under the aegis of the NIH. This Center helps pharmaceutical companies, various research institutes and non-core organizations to find a general solution, which will allow prospective studies to successfully complete stage T1, which is often called "Death Valley" due to the fact that many potentially practically applicable substances remain only within this stage's framework. Most companies put only a part of a multitude of the generated molecules to good effect. Other molecules remain at the project stage only; however, these projects are owned by the manufacturers. The NCATS suggests accumulating the non-realized projects in order to establish collective intellectual property, which will allow institutes and small companies to put to good effect and improve the already generated chemical substances. The Center also facilitates drug's completion of other stages of the translational research until entry into the market; this includes interaction with governmental institutions. The NCATS controls activity of all its agencies, accumulates and distributes the funds received from the government and various organizations and draws reports, which make flow of funds along the study stages transparent to general public [29].

Collaborations for Leadership in Applied Health Research and Care (CLAHRC) – an initiative established in Great Britain. It consists in coordination of activity and information exchange between different organizations, which directly and indirectly participate in translational research – research institutes, universities, laboratories, local healthcare establishments (hospitals, foundations), local public authorities, charitable foundations and ethics committees. The CLAHRC is aimed not at intensification of work of specific structures, but at construction of a common organizational model, which will facilitate interaction of different departments and reduce time and cash expenditures required for successful completion of all the stages of a translational study [30].

Translational research in the Russian Federation

The history of translational medicine in Russia began in Saint Petersburg in the beginning of the XX century. I.P. Pavlov and other scientists performed translational studies, which were closely linked with clinical practice, at the Institute of Experimental Medicine. Physiologist I.P. Pavlov took part in the activity of the neurosis hospital as a consultant. Results of his studies, which were performed on laboratory dogs, were introduced into therapeutic practice. Thus, patients in Saint Petersburg were treated with canine gastric juice at that time [31].

The Ministry of Health of the Russian Federation has developed the Strategy of Medical Science Development until 2025; it was adopted by the Government of the Russian Federation on 28.12.2012. The document draws specific attention to the development of translational medicine in Russia. It is planned to establish special translational research centers, develop research institutes and laboratories at universities around the country and elaborate roadmaps for planning medical technologies. The Strategy implementers will set priorities and coordinate implementation of scientific-technical projects with the ultimate goal of application thereof in clinical practice [32].

Translational Research and Personalized Medicine Laboratory was established at the Moscow Institute of Physics and Technology in 2012. Its primary spheres of activity involve discovery of new oncological markers and target gens for therapy and development of a tumor diseases diagnosis program. Innovation campus "Skolkovo" has been being built since 2010. This project involves many pharmaceutical and biotechnological companies, laboratories and medical centers. They will develop new technologies and therapy methods (which will in many cases be established from scratch) and introduce them into clinical practice.

NIF Foundation established the Initiative on Russian-American Cooperation in Biomedical Research in the framework of the Russian-American bilateral Presidential Commission in 2009. Cooperation is aimed at two vectors: annual forum conferences for interaction of scientists from Russia and the USA and training courses conducted by the US NIH Clinical Center for Russian

scientists. Thus, "Training for clinicians and specialists in translational medicine" for specialists from the Russian Federation and the USA was held in 2011 at the Kulakov Center for Obstetrics, Gynecology and Perinatology. The first Russian-American conference on brain sciences was held in Washington in the same year in the framework of the Russian-American Scientific Forum. There is also cooperation in the sphere of joint projects, such as "Preclinical analysis and prevention of neurodegenerative diseases", "Concurrent pluridirectional tumor treatment" etc. [33].

CONCLUSIONS AND RECOMMENDATIONS

Translational research has helped to bring together scientific studies and application of results thereof in clinical practice. In recent years, TR has made a huge step forward, including development of new technologies and methods of assessing medical innovations in terms of application thereof in the most appropriate spheres [34]. International development of translational medicine has become true owing to establishment of new centers, elaboration of special state and international programs for translational medicine development and clinical training of medical personnel on the basis of results of the performed studies. Most likely, future TR development will be aimed at faster completion by new projects of all the research stages and improved effectiveness of selection of promising drugs and technologies. Another important objective of TR is the search for ways of applying the newest technologies in different spheres of science and practice, including, but not limited to, medical practice. If the Russian Federation plans to take part in the international trends, it must without any doubt develop translational research at Russian scientific centers.

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