

Bioethical Aspects of Translational Medicine

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Abstract: The development of modern medicine is associated with the dynamic translation (transfer) of basic medicine data to clinical research and further on to clinical practice. It is pointed out that research and development in the sphere of genetics and biotechnology, which are of particular significance during the COVID-19 pandemic, are of paramount importance in this regard. The concept of "translational distance" is analyzed as a measure of uncertainty, namely, the number and the size of logical leaps in course of transition from animal model trials to the first stages of human subject research. Translational research ethics has become a revolutionary, diverse, and distinct field of biomedical ethics. When studying the issue, special consideration is given to the critical blocks in translation as well as the characteristic features, types, and phases of translational research. It is emphasized that addressing the issue of minimizing irreducible uncertainty so that research participants could participate in research is a key component of ethical research. In view of the fact that the most important condition for the successful implementation of translational medicine is the adherence to the principles of bioethics when overcoming translational distances is analyzed taking into account the benefit-risk balance. As the development of translational medicine is significantly influenced by the legislation and the practice of its application, the national peculiarities of the attitude of different countries to the issues of ethics and the resolution thereof are studied, including the differences between the continental and the Anglo-

Saxon legal families. Along with the formation of a general approach to the choice of a regulatory model in the sphere under consideration, the acceleration of circulation of the information related to science, research and technology, as well as the rapid obsolescence of innovations, should not be overlooked. At the same time, one should pay attention to the existing biological and other risks.

Keywords: translational research; translational distance; translational blocks; bioethics

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I. Introduction

The rapid development of bioethics is the most impressive sign of a qualitative change in ethical knowledge, science and culture in general. It has now become common to refer to research — especially the research using new biotechnologies and genetic technologies — as “translational.” This term helps to illustrate the need for and the value of analyzing all health-related research (Ashikhmin, 2015; Sychev, 2016).

The need to remove barriers (in the sense of acceleration of introduction of the basic [fundamental] science achievements into clinical practice) determined the birth of translational medicine (Seals, 2013) as a research methodology (Ashikhmin, 2015) in the early

1990s. “Translationality” is an approach consisting in the transfer [or translation] of research results (often of a basic nature) into the actual clinical practice for the benefit of patients (Sychev, 2016).

Translational research is broadly described as “knowledge transfer,” *i.e.*, the transfer of knowledge from laboratory research to clinical practice, public healthcare, and policy, and vice versa, resulting in enhancement of the methods of diagnosis, treatment, and prevention. One of the challenges facing translational research is the high pace between a discovery and its development and implementation, which has become especially relevant during the COVID-19 pandemic. It is essential to point out that the most important condition for the successful implementation of translational medicine is the adherence to the principles of bioethics. The development of the translational medicine concept is largely associated with consequentialism — a trend in Western philosophy. Consequentialism (derived from consequent [Latin *consequens*, meaning “consequence, conclusion, result”]) is understood as a set of moral theories where the criterion for moral assessment [judgement] is the result (with regard to the topic in question this would be the research result) (Khokhlov *et al.*, 2021). From the standpoint of consequentialists, an action or inaction is morally right when it produces good results or consequences. Consequentialism is usually contrasted with deontological ethics (which has an ancient history) where rules and moral duty are central. According to this system of views (sometimes opposing), the most important thing is an appropriate balance of benefits and risks for research participants and for society as a whole. Upsetting this balance may lead to negative consequences in the future which are not always easily predictable — therefore, a detailed review of bioethical issues with regard to translational research is required.

II. Definition and Characteristic Features of Translational Medicine

One of the key issues of translational medicine is the elimination of critical blocks in translation (transfer and implementation of scientific concepts in a new environment). The main of such blocks are:

- the block between basic science (research) and clinical research;

— the block between clinical research and the implementation of a particular treatment method at the system level.

Noteworthy, in addition to a direct “translation,” there is also a reverse one — *e.g.*, the use of data obtained during clinical studies in the search for new targets (Ashikhmin, 2015). Overcoming these conventional blocks or barriers is in many respects connected with the issues of bioethics.

The following areas related to translational medicine should be distinguished: basic research; evidence-based medicine; biomedical ethics; public health; healthcare economics (Ashikhmin, 2015).

The characteristic features of translational research are as follows:

1) operation “at the junction” of several spheres of knowledge with blocks impeding the “translation” between them;

2) the need to formulate a scientific (research) hypothesis before the start of each of the stages of the experiment or analysis with verification of the correctness of the concept after the completion of each stage;

3) assessment of the clinico-economic, financial or medico-social feasibility of development.

Thus, the difference between “scientific methodology” in its pure form and translational medicine lies in the fact that the latter is focused on a specific result with direct consideration of financial and market factors.

It would be incorrect to directly compare translational medicine to “evidence-based medicine” — although the former uses the evidence-based medicine methodology, it is not limited to it.

The translational approach is very actively used in the development of personalized (individualized) treatment — hence they are often mentioned in the same context. At the same time, “evidence-based” individualized treatment (usually based on the achievements of genetics) should be distinguished from individual healthcare which is based primarily on empirical experience and often runs counter to clinical recommendations.

The following types of translational research can be distinguished (Khokhlov *et al.*, 2021):

1) basic research studying the biological effects of drugs used in humans;

2) researching the disease “biology” (pathomorphology, pathobiochemistry, *etc.*) in sick people with the purpose of searching for new methods of treating diseases (*e.g.*, searching for mutations in the genes of tumor cells that can serve as targets for targeted drugs);

3) non-clinical (most often preclinical) research with the purpose of introducing a particular treatment method into clinical practice or determining the principles for therapeutic intervention (*e.g.*, the study of the antimicrobial and antitumor effects of thalidomide on biological models in the 1990s despite the thalidomide tragedy associated with the teratogenic effect of the drug);

4) any clinical research initiated based on the results of the work referred to in points 1–3, including those for evaluation of toxicity and/or efficacy;

5) integrative analysis and research with the purpose of overcoming the block impeding the translation of research into real clinical practice within the framework of the so-called “science-for-business” research.

Along with that, the term “translational research” is used in a narrow sense to refer to a correctly planned way of treatment method development at various stages of clinical research.

The distinctive features of the translational approach are its integrativity (with upfront research in related fields), verification of the concept correctness after the completion of each stage, as well as performance of a new round of research on biological models when the side effects or therapeutic effects are detected at the early stages of clinical research (Ashikhmin, 2015).

It should be pointed out that, at the moment, increasingly more research publications are attributed to the sphere of “translational” research, but in fact do not pertain to this sphere (for instance, due to the fact that the concept of the treatment method studied by clinicians did not come from a basic research laboratory, but was born in course of a previous clinical study and has never been tested on biological models). Likewise, the most part of basic research where a working hypothesis indicating a specific point of application of the research results in disease treatment was not initially formulated cannot be considered translational research (Ashikhmin, 2015).

Translation should not mean assuredness [confidence or certainty] that the research direction will lead to creation of safe and effective medications or treatments. It is important to keep in mind that, at any stage, the results of well-planned and correctly conducted research may lead not forward, but backward, or in a completely different direction, in order to elaborate (add precision to) and expand knowledge at an earlier stage, or to explore and develop the newly discovered opportunities.

III. Phases of Translational Research

Researchers should have the responsibility of thinking about the future directions of research, foreseeing the relationship between the research design and the research ethics, as well as reviewing and — from time to time — revising the way of conducting research which has scientific and social value, regardless of the direction taken along the translation path from one experiment to another.

The issues of bioethics are often not considered before human subject research, however, there are many issues that deserve attention even when conducting basic research. These include: data integrity, responsible reporting and dissemination of results, as well as ensuring that each study is designed and conducted in such a way that it can yield results suitable for deciding on the next stages of research (Joffe and Miller, 2008).

The use of animal models in preclinical trials remains a necessary stage for the success of future clinical studies. Attempts are being made to minimize the use of animals, however, the potential alternatives — such as computer modeling and body-on-a-chip¹ organoid arrays — have significant limitations and require further development (Esch *et al.*, 2011). Therefore, researchers must take into account the three key principles of testing in animal models (the so-called “3Rs” concept): replacement, reduction, and refinement. The choice of animal models, as well as humane treatment and appropriate use thereof, help to ensure that the principle of “modest translational distance” — a term introduced

¹ Body-on-a-chip — integration of several organoids on a chip.

by Jonathan Kimmelman (Kimmelman, 2009) — is respected in course of research transition from animals to humans.

Translational distance is a measure of uncertainty, namely, the number and size of logical [inferential] leaps in course of transition from animal model trials to first-in-human research.

At the early stages of research involving human subjects, the modest translational distance may provide an analytical model for considering the relationship between research design and ethics. In such instances, this role cannot be performed by the concept of clinical equipoise. This concept can only be applied to later-stage research, such as trials comparing experimental interventions to standard treatment. Clinical equipoise justifies asking patient-subjects to take the risk of receiving unproven intervention in clinical trials. Early-stage research cannot offer the potential for direct benefit to patient-subjects that may be available in later-stage research. Instead, modest translational distance justifies asking patient-subjects in early-stage research to risk receiving an unproven intervention only when the “inference gap” is small enough to predict that the clinical trial can yield useful results. Modest translational distance should guarantee the safety of study participants, which is of paramount importance (Baker *et al.*, 2016).

In order to move from preclinical to first-in-human and other early-stage clinical trials, the principle of an appropriate balance between the risk of harm and the potential benefit must be addressed. This approach applies at all stages of clinical research, but is particularly important in the early stages, because what counts as potential direct benefit to patient-subjects in these trials is limited or — at best — unclear.

In early-stage research, this question is more appropriate than the question “Have the risks of harm been minimized?”, as it acknowledges that some risks of harm are still unknown and that it is never really possible to eliminate all uncertainty.

Addressing the issue of minimizing irreducible uncertainty so that research participants could participate in research is a key component of ethical research. Like the more familiar Belmont Report requirement that risks of harm and potential benefits “must be balanced and shown

to be in a favorable ratio” (The Belmont report, 1978), this reasoning forms the basis of productive discussions between researchers, their colleagues and regulators, sponsors and ethics committees.

IV. Ethical Issues of Translational Research

The two key considerations that relate the design of clinical trials to research ethics considerations are scientific validity and social value.

Correct research is methodologically rigorous; it is designed and aims to provide useful answers to the questions it asks — including negative answers.

Research value is usually defined as a progressive value, which implies the likelihood of research progression to its next phase (Emanuel *et al.*, 2000).

However, first-in-human and other early-stage research is also likely to have translational value that is not progressive, but may be reciprocal, iterative, or collateral (Kimmelman, 2009).

Reciprocal value highlights the need for new preclinical trials (also due to getting certain results that need to be clarified).

Iterative value helps to enrich the clinical trial itself by providing new data that can be productively used for in-trial modifications as the trial goes forward.

Collateral value helps one or more different trials by producing new information, gaining experience, and developing methods for researchers in related research or related fields. Researchers who recognize the broad applicability of study data and design translational research to take advantage of many different types of value can readily plan both to eliminate what would otherwise simply be regarded as failures of research progress and to enhance the value of successful research.

Selecting patient-subjects from whom scientifically useful data can be collected and who are also able to make well-informed choices regarding their participation in research is especially important in early-stage research. Choosing the population from whom the most knowledge may be gained and who also can most readily be helped to

make autonomous choices about participation may be challenging, as sometimes those are two different groups of potential patient-subjects.

Researchers should take care to provide reliable (accurate) information, not only to potential subjects in the form and process of obtaining informed consent, but also to the mass media and in publications discussing study results.

Objective high-quality information reduces the likelihood that the “therapeutic misconception” will cause potential subjects, their families, regulators, the media and the public, and even fellow researchers, to overestimate the potential benefits of the research or underestimate the risks of harm. The need for long-term follow-up, both to monitor the health and function of patient-subjects after the intervention and to determine the intervention’s success or failure, is often overlooked, not only in study planning and budgeting, but also in disclosure to potential research subjects.

Of course, well-designed translational research has value even when ultimately unsuccessful. Failure in a well-designed first-in-human study supports investigating potential reciprocal, iterative, or collateral value. Reciprocal value could be finding out that patient-subjects with a pre-existing disease react differently from other patient-subjects, leading to a preclinical study done in animals with that condition. The procedural nuances necessary for success may have iterative significance in first-in-human trials. For example, surgical techniques may be improved considerably from one patient to the next within a single protocol and many other in-trial procedural modifications (*e.g.*, special postoperative treatment, specific exercise, bed rest protocol, or specialized physical therapy). Finally, the involvement of a large number of medical specialists is by itself an additional value that is of great importance for further practical implementation of the research results.

Thus, research that can identify potential reciprocal, iterative, and collateral value may prove productive — despite some failures — providing hope that the research may be continued through additional clinical trials.

For the researched intervention to become a successful treatment, it has to function better than the standard treatment. Yet what does

that mean in terms of defining success? On the one hand, it could be reasonable to expect that the researched intervention would ultimately prove to be a panacea, but on the other hand, what if the researched intervention transforms a progressively fatal disease into a chronic one? If partial functional correction is an acceptable goal, then the researched intervention might be introduced into the treatment arsenal as another useful “halfway” medical technology that is not a panacea. A researched intervention that meets this goal of partial functional correction could reduce the need for the relevant therapy.

Financial conflicts of interest are a critical ethical issue commonly encountered at the pre-approval stage of translational research. Profound financial interconnection between sponsors and researchers can interfere with work due to issues such as patenting. Such conflicts can lead to non-disclosure of information about risks to participants and negative results in publications.

In the era of translational research, social injustice is one of the most relevant ethical concerns. It is common for resource-rich countries to conduct translational medical research in countries with limited resources, and if the results of the research are not expected to be useful or are expected to be less beneficial to the country with limited resources, the problem of social injustice arises.

The data generated as a result of each phase of translational research, particularly in the early stages, are vulnerable (sensitive) due to possible ethical issues related to data confidentiality protection.

Sharing research data at inappropriate stages of research can lead to the risk of early unauthorized implementation leading to dangerous consequences, such as the untoward adverse effects or even bioterrorism.

The development of translational medicine is significantly influenced by the national legal system, by the legislation and the practice of its application. The attitude of a state to the issues of ethics and to the resolution thereof has national peculiarities. As for the continental legal family (that is based on written law, on the legal norms adopted by the state and maintained by its enforcement mechanisms), ethical as well as bioethical norms has had little impact on the legislation and the practice of its application. They were generally considered as auxiliary (along

with the norms of morality, religion, and some other norms), and their application was of a subsidiary nature.

In the Anglo-Saxon legal family, the role of ethical norms has been higher due to the precedent-based nature of some cases and judicial decisions made. The argumentation and substantiation for the rulings rendered by courts and other jurisdictional bodies were based not only on the norms established by the state [government], but also on other norms developed by professional communities or other groups and precedents as such (previous decisions made with regard to similar cases).

The widespread development of civil, corporate and other kinds of relations in Russia, including self-regulation and self-government, as well as the formation of new spheres of activity (*e.g.*, clinical research of pharmaceuticals, clinical trials of medicinal products), required reception of the best practices of other countries by Russian legislation and practice. The development of practical (applied) bioethics was no exception. Its norms, lying in the borderline area between legal and other regulators, undoubtedly, influence the development of translational medicine.

This influence manifests itself at several key stages: the transition from basic [fundamental] knowledge to applied knowledge; the obtainment of a practical result (innovation) based on the existing new knowledge; the transfer of a technology (a new product or item) to the healthcare sector.

The development of both basic and applied science is the stage least regulated by legislation or by ethical and other norms. On the one hand, the government is eager to support scientists/researchers and research activities in every possible way, as well as to encourage the growth of scientific knowledge. On the other hand, already at this stage, results of a dubious nature in terms of research ethics, bioethics, or the ethics of the professional community, may appear. Moreover, some intellectual activity results may remain without legal protection if they contradict legal norms, or if they are contrary to public interests, or the principles of humanity and morality (paragraph 4, Article 1349 of the Civil Code of the Russian Federation).

In some countries, already at this stage, the potential ethical and ethico-legal issues are resolved by the dedicated local ethics boards (committees) at research organizations, or ethics boards functioning in science and research communities. In Russia, such structures exist, but not everywhere, as they are not mandatory by law.

Article 10 of Federal Law No 127-FL of 23.08.1996 “On Science and State Science and Technology Policy” it is worth noting in this regard. According to it, the procedure for conducting research may be established by the Government of the Russian Federation. Some kinds of research activity may also require a license.

The ethical and ethico-legal regulation for the stage aimed at creation and subsequent implementation of a new technology (product, item) is somewhat better developed. Quite stringent administrative and other requirements have been established for preclinical and clinical research (trials) of pharmaceuticals, medicinal products, and clinical testing. At this stage, sector-specific ethics boards — currently under the Russian Ministry of Healthcare — are an obligatory element of the approval system even in relation to individual technologies (products).

Despite their long-term functioning and extensive working experience, they are still facing certain difficulties due to the insufficient degree of their institutionalization in Russia, as well as due to the uncertainty of their individual rights and obligations. Further institutionalization of such boards within the Russian legal space will require amending the existing federal laws that govern the circulation of pharmaceuticals, medicinal products, *etc.*

The stage of technology (new product or item) transfer to the healthcare sector typically requires legal rather than ethical regulation. The sector should be ready to accept a new technology or product, which requires not only organizational, financial and other resources, but also timely changes in the legislation governing public healthcare, government/municipal procurement, *etc.*

Backward translation is also important for the development of medicine. The data obtained during research (such as side effects, risks, *etc.*) is of great significance for science/research and the development of the sphere as a whole. It allows to avoid mistakes, reproduce someone else’s experience, *etc.* This requires data transparency (publicity)

that can be provided only through placing the obligation to disclose information as established by the federal law on the persons/entities conducting relevant research or on the state regulator in this sphere.

Feedback is important for science/research and practice, as well as (in case of the so-called “post-marketing research”) for identifying the side effects of new technologies or products. It can also be provided through administrative regulation, control (supervision) over the circulation of certain technologies and products. Ethical norms, including those of professional ethics, can play a supporting role here. The priority of the interests of the patient and society is higher than the interests of business or individual entities.

Currently, Russia is seeking to create an optimal regulatory model based on studying the operational experience of Russian ethics boards, as well as the experience of the countries (primarily, those belonging to the continental legal family) where the activities of ethics boards at various levels are sanctioned by the legislator, and where there are positive results of ethical and ethico-legal support at the critical stages of activities mediating the relations in the sphere of translational medicine.

Along with the formation of a general approach to the choice of a regulatory model in the sphere under consideration, the acceleration of circulation of the information related to science, research and technology, as well as the rapid obsolescence of innovations, should not be overlooked. In addition, the model needs to take into account the existing biological and other risks that did not disappear with the development of humankind, but remain tangible nowadays. In this connection, in our opinion, it is important to create a model not only for the development of translational medicine in the current, common, ordinary conditions, but also for accelerating its development in the most significant areas. An independent problem requiring a prompt solution is, currently, the elaboration of a work model, which is balanced and adequate to the existing threats or risks, for scientists, innovators, business people, officials, and members of ethics boards during natural or technogenic emergencies. The new coronavirus pandemic has revealed the challenges existing in the development, research, and testing of pharmaceuticals (including vaccines), medicinal products and other items used in medicine.

V. Conclusion

Translational research is of great importance for the implementation of basic scientific knowledge in public healthcare. At the same time, the implementation of basic research results in medical practice has been going on for a long time. A new look at this issue and the concept of translational medicine are connected with the fact that the speed with which discoveries made in laboratories are introduced into medical practice and healthcare has now increased significantly. And this poses new tasks for bioethics. Translational research ethics has become a revolutionary, diverse and distinct field of biomedical ethics. Insights in various ethical issues are necessary to identify potential risks and prevent unethical practices while such research process is undertaken. The well-being of research participants and society should be prioritized over advancement of knowledge. At the same time, in the context of the new coronavirus pandemic, new trends are starting to emerge when the risks for the trial subjects are becoming quite high. An example of this approach could be the research at an artificial infection clinic in the UK. This highlights the necessity of discussing various types of ethical issues, which over time become the basis for the preparation of legal documents and professional guidelines needed by scientists when conducting translational research.

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