THE ACTIVITIES OF THE LOCAL ETHICS COMMITTEE TO IMPROVE THE QUALITY OF BIOMEDICAL RESEARCH OF YOUNG UNIVERSITY STAFF

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The article is devoted to the issues of clinical research: their ethical and legal regulation at the present time, the history of ethical expertise in the Russian Federation and at Kazan State Medical University. The role of ethical committees as a structure responsible for quality of scientific research and a guarantor of compliance with the principles of ethics, protection of the rights, safety and well-being of research participants is considered. The article presents the working experience of the local ethics committee of Kazan State Medical University on ethical examination of research projects with human participation and analysis of the most common mistakes in preparation of research documentation made by young scientists of clinical departments. The digital information showing typical errors and inaccuracies in the formation of a package of documents for ethical examination, based on the analysis of 284 initiative papers of PhD candidates from clinical departments: every fifth protocol required revision in accordance with the ethical and legal framework adopted in the Russian Federation, in 1.5% of cases the documentation was submitted for already conducted studies (i.e. ost factum), when no changes to its design are possible anymore. Typical mistakes were the following: inability to form research and control groups, calculate a representative number of participants, write an information sheet for a participant in a clinical trial and a sheet of informed consent, going beyond the specialty, desire to prescribe drugs beyond the scope of registered indications, etc. The ways of increasing both the awareness of young researchers and quality of ethical expertise by specialists of the ethics committee are proposed.

Keywords: biomedical research, ethical committees, ethical expertise, clinical trial protocol

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ДЕЯТЕЛЬНОСТЬ ЛОКАЛЬНОГО ЭТИЧЕСКОГО КОМИТЕТА ПО ПОВЫШЕНИЮ КАЧЕСТВА БИОМЕДИЦИНСКИХ ИССЛЕДОВАНИЙ МОЛОДЫХ СОТРУДНИКОВ УНИВЕРСИТЕТА

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Статья посвящена вопросам клинических исследований: их этико-правовой регламентации в настоящее время, истории становления этической экспертизы в Российской Федерации и в Казанском государственном медицинском университете. Рассмотрена роль этических комитетов как структуры, несущей ответственность за обеспечение качества научных исследований и гаранта соблюдения принципов этики, защиты прав, безопасности и благополучия участников исследования. В статье представлен опыт работы локального этического комитета Казанского государственного медицинского университета по этической экспертизе исследовательских проектов с участием человека и разбор наиболее часто встречающихся ошибок при оформлении документации к исследованию, которые допускают молодые ученые клинических кафедр. Представлен цифровой материал свидетельствующий о типичности ошибок и неточностей при формировании пакета документов для этической экспертизы, основанный на анализе 284 инициативных работ диссертантов клинических кафедр: каждый пятый протокол требовал доработки в соответствии с этико-правовой базой, принятой в Российской Федерации, в 1,5% случаев документация была представлена на уже проведенные исследования (т.е. post factum), когда никакие изменения его дизайна уже невозможны. Типичными ошибками явились следующие: неумение формирования исследовательской и контрольной групп, расчета репрезентативного числа участников, написание листа информационного листка участника клинического исследования и листа информированного согласия, выход за рамки специальности, желание назначения препаратов за рамками зарегистрированных показаний и др. Предложены пути повышения как информированности молодых исследователей, так и качества проведения этической экспертизы специалистами этического комитета.

Ключевые слова: биомедицинские исследования, этические комитеты, этическая экспертиза, протокол клинического исследования

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Clinical trials (CT) in the Russian Federation have been regulated for less than a century and are based on the best international practices. Ethical recommendations for CT were laid down by the Nuremberg Code (1947*)* [1] and the Helsinki Declaration of the World Medical Association (1964) [2]. Each country had its own unique rules for this process and in order to register a foreign medicinal product (MP), full-scale tests on the territory of this country had to be conducted. The unification of requirements to CT was initiated in 1996 with the release of the first harmonized rules of Good Clinical Practice (ICH GCP), which set out the agreements in Europe, USA and Japan on the harmonization of legislation in the field of CT and elimination of obstacles to register drugs in different countries, which led to a cheaper product for the consumer due to mutual recognition of the CT results [3].

After adoption of general rules, the process of harmonization of the legislations of different countries was accompanied by the appearance of documents of the Interparliamentary Assembly of the Confederation of Independent States (Eastern Europe and Central Asia); UNESCO; WHO [4–6].

Russia has actively joined the global process. In our country, the legislative framework in the field of CT and drug registration has been fully formed by the end of the last century [7]. For the sake of fairness, it should be noted that

before adoption of the ICH GCP in the USSR, there was a pharmacovigilance system that functioned from 1969 to 1991 and regulated, among other things, the field of clinical research, perhaps even more strictly than the international standard [8]. A significant milestone in development of ethical and legal support for biomedical investigations (BMI) was the creation of a system of ethical expertise with the participation of ethical committees (EC), whose legitimacy was recorded in 1993 in Federal Law No. 5487-1 "Fundamentals of Legislation of the Russian Federation on public health protection". The first ECs at the level of hospitals and research centers (local ethical committees, LEC) were established in the mid-90s. In 1998, the Ethics Committee at the Federal Agency for Quality Control of Medicines under the Ministry of Health of the Russian Federation began to function. The Central EC was actually part of the control and licensing system of the Ministry of Health of the Russian Federation, since in order to obtain permission from the Ministry of Health to conduct a clinical trial, a positive conclusion of this Committee was required. Later, this role was taken over by the Federal Service for Surveillance in Healthcare (Roszdravnadzor), and in 2004, a committee was established within the body issuing approvals for the planned multicenter research.

Since 2010, according to the law "On the Circulation of Medicines", permission for the entire turnover of medicines in the country was provided by the Ministry of Health of the Russian Federation.

Thus, a vertical appeared: federal EC — local ECs. For local ECs, our country has adopted the European model, in which they have a public character and advisory powers [9].

The next step in development of the system of ethical committees was adoption of legislative acts that consolidated the basic principles of CT, standards for planning and conducting BMI, registration and presentation of their results at the state level. It guarantees protection of rights, safety, well-being of research subjects and ensures BMI quality. Today, these ethical structures exist in all major research centers where BMI of different levels are conducted (multicenter and local, initiated by foreign and domestic sponsors, initiative research), they ensure compliance with the GCP rules. The EC activities are based on three principles:

- respect for the personality and rights of the patient;
- predominance of benefit over risk and risk minimization;
- the correct selection of patients to participate in the study.

The first and most important right of the human involved in scientific research represented by voluntary informed consent is enshrined in Article 21 of the Constitution of the Russian Federation, all principles are reflected in current Federal laws such as Federal Law No. 323-F3 "On the Basics of Protecting the health of Citizens in the Russian Federation" (2011), No. 61-FZ "On the Circulation of Medicines" (2010) and others [10].

The history of the EC emergence in the Republic of Tatarstan, a subject of the Russian Federation, is as follows: in 1998, the republic adopted its own law "On the protection of Citizens' Health", where article 14 referred to the possibility of creating an ethics committee (commission) in the healthcare system, which gave rise to the development of a package of documents related to the creation of the EC, and in 1998, by order of the rector of the Kazan State Medical University, the first EC appeared in the Republic of Tatarstan, which was given the republican status in 2003. This committee set goals not only for the ethical examination of BMI conducted at its bases, but also for the protection of patients' rights in the practical healthcare system, under conditions of compulsory medical insurance and availability of the private medical services market (in fact, it combined tasks and functions of the research and hospital committee based on the experience of foreign countries), and also pursued the task of uniting ethical structures in the republic, personnel training according to GCP standards adopted by our country. In 2006–2008, our EC successfully passed the accreditation procedure by the World Health Organization with a three-stage program "Recognition" (Inspection WHO and program the recognition for the ethics committee), which included both an educational component by WHO experts, and an audit of internal documentation (standard operating procedures), an inspection of the work of the EC and its certification. It should be emphasized that we have become the first ethics committee in the Russian Federation to receive such recognition. Later, when Russia broke into the international CI market, with the increase in the number of BMI at the bases of the Kazan State Medical University, committees were divided by functions into republican and newly created local ones (2009) [9].

We are proud to note that Kazan State Medical University was one of the twenty most involved in international multicenter clinical trials (IMCT) research centers in Russia (fourth in 2015, third in 2016 and 2017, fifth in 2018 and 18th by the end of 2019). Even during Covid 2020 pandemic, our republic demonstrated an increase in the number of studies of new IMCTs (101 in 2020 against 71 in 2019, an increase of 42%) conducted on its territory, and the Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan (Kazan) took the 11th place in the TOP 20 medical organizations in terms of the activity of participation in the IMCT approved in 2020. In recent years, due to the difficult geopolitical situation in the Russian Federation, multicenter clinical trials of foreign sponsors have practically not been conducted, the BMI market has been reoriented to local research, mainly represented by bioequivalence studies of generics and biosimilars, which is implementation of the state import substitution program announced by the president of the country. The relevance of initiative research has increased many times. In this regard, the activities of the LEC of the Kazan State Medical University are largely reoriented towards them [11].

Over the 15 years of our EC work, the number of initiative research projects has not changed significantly and amounts to an average of 60–75 projects per year. A significant failure occurred only during the Covid 2020 pandemic, which was due to restrictions in contacts between researchers and patients. Most of the university's initiative research is traditionally carried out by young researchers during the postgraduate training, which provides for the acquisition of research skills by applicants. In preparation for the exam in the history and philosophy of science, where bioethics issues are discussed, students at our university are taught questions of research ethics — the ethics of working with an experimental animal (mainly for postgraduate students of theoretical departments) or with a human participant in a clinical study (for postgraduate students of clinical departments). Young scientists are taught to choose the design of the study, calculate the number of participants in the experiment so that the results obtained could be representative and meet the requirements of evidence-based medicine, choose methods and strategies for data collection, draw up a protocol, issue patient information sheets and informed consent sheets for study participants, select statistical analysis methods according to the tasks and features of scientific material, ensure the quality of research, identify key procedures, work in a team, manage the data

obtained, prepare reports and publications, properly prepare documentation at all stages, etc. Writing a research protocol with discussion and defense in a group of colleagues is part of the training. We are experienced in interacting with researchers in the framework of additional professional education under the GCP (Good Clinical Practice) and Good Biomedical Research Practice (GBRP) programs, organized by WHO, the Regional Training Center for Scientific Research in Healthcare (RC NIH, Astana, Kazakhstan) and the Kazan State Medical University (Russia). We offer the best available practices to young scientists [11].

After approval of the topic of the dissertation research and graduation, postgraduate students bring their research projects to the LEC, which examines the package of documents for the planned research and approves or justifiably rejects it. The results of internal quality control of the educational process showed 89% satisfaction of postgraduates with this issue.

Unfortunately, unlike commercial research projects written and verified by professionals, initiative research often reveals certain inconsistencies with the ethical and legal standards of this field of activity. In 2023, we analyzed 284 initiative works of PhD candidates of clinical departments of the Kazan State Medical University, identified errors and shortcomings in the documents and established the following: every fifth study, or rather 21.1% of the packages of clinical research documents submitted to the LEC, planned at the university as theses, does not meet the requirements accepted in our country. About 1.5% of the work is submitted to the EC after completion of the study, when no changes to its design are possible. Among the works reviewed during the specified time period, LEC rejected one work on this basis.

According to experts, when conducting an ethical examination of initiative projects, the same type of errors was encountered. The most frequent comments of EC experts were related to the fact that the presented protocol does not substantiate or insufficiently substantiates the sample of patients, comparison groups are carelessly formed (according to the analyzed parameters — age, gender, social status, etc.), which reduces the value of the work and significantly affects its conclusions. Researchers often describe their work as non-interventional trials, but actually work with the documentation of a medical institution retrospectively and/or their research is purely observational/non-interventional. And conversely, a young scientist has a great desire to test a well-known medicinal product off-label, in a dose or in a mode different from that prescribed in the leaflet.

Although such a study may pose a danger to its participants, such initiative projects, as a rule, do not provide insurance for CI subjects and strict reasonable health monitoring. In fact, this is a phase II CI, and strict GCP requirements are imposed on it [12]

Errors are often found in the registration of the patient's informed consent to participate in the study. The young scientist does not share the standard of medical care provided in a medical organization (MO) and his clinical investigation (CI), believing that if he needs standard hematological or biochemical health indicators of the observed patient for analysis, then this is all about the research work. At the same time, when hospitalized in the MO (inpatient) or during an outpatient visit (polyclinic), the patient signed an informed consent for standard medical care, and repeated consent is not necessary.

About 6% of young researchers believe that if blood sampling for their project is combined with the collection of biomaterials (for example, blood) of a patient according to a standard treatment protocol, then the consent of the participant to take an additional sample is not required. The standard of treatment of a patient in a medical institution and participation in scientific research are different things. Each participant in a clinical trial should be clearly understand that he is offered the procedures that are not included in the standard of medical care, and that he agrees to them voluntarily, without coercion, understanding the value of this research for himself and the development of science. Accordingly, the information sheet of the CI participant should contain in an accessible form all information about the planned work and clearly prescribe each step of the study, and informed consent should contain only information that relates to this initiative study, and not to all procedures that await the patient/patient at this stage of receiving medical care.

In a number of works, the researcher decides to cross the threshold of his competence and, being, for example, an obstetrician and gynecologist, decides to investigate the cognitive functions of the patient. As a result, he makes a judgment about the presence of the disease and even suggests its correction [12], which is fundamentally wrong and unacceptable.

It is particularly noteworthy that every year more and more comments relate not to the substance of the work, but to its design: negligence in writing documents, when different numbers of expected participants are indicated on adjacent pages of the same document or in different documents of the same package; the criteria for including and excluding patients from the study do not match; in protocols and information leaflets, manipulations with biomaterial are described in different ways, etc. We can also see that postgraduate students have a formal attitude to obtaining LEC approval: they copy other people's documents without understanding the essence, which results in comments from experts and request to finalize documentation. But this is no longer a question of knowledge of principles, rules and standards, but a question of attitude to the work performed [12].

Thus, the local ethics committee sees its mission in improving the quality of research conducted on the territory of its supervision in the education of young people (educational component) and in protecting the rights of patients (thorough examination of submitted projects). The first is carried out by improving the quality of teaching bioethics and medical law at the pre-graduate stage, research ethics issues at the postgraduate stage, involving students in the process of participating in Olympiads, grant events on medical ethics and biomedical research. The second is to improve the skills of the experts of the ethics committees both through internal training based on the materials of clinical databases and external training based on GxP cycles. In the last year, it has become extremely useful to conduct the School of Ethics of Scientific Research, an initiative non-profit educational project for young Russian researchers and members of ethical committees aimed at creating a high level of research culture necessary to achieve national goals and scientific and technical development of the Russian Federation, initiated by the Rector of the Yaroslavl State Medical University Kokhlov AL and Chairman of the Interuniversity Ethics Committee, Chairman of the Independent Interdisciplinary Committee for the Ethical Examination of Clinical Trials Volskoy EA on the basis of the National Research Institute of Public Health named after Semashko NA" The project has not been completed, it will continue during the next academic year. It is attended by leading experts in the field of clinical research, and their recorded lectures are invaluable material for the younger generation.

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