THE ROLE OF AN ETHICAL REVIEW IN PEDIATRIC CLINICAL TRIALS

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The article discusses the role of an ethical review in clinical research involving minors. It examines the historical aspect of the ethical component of clinical trials involving minors. The article analyzes the legislative regulation of clinical trials involving minors in Russia and internationally. Currently, the need in pediatric trials is not a point for dispute. It is the issues of optimization of planning and conducting pediatric trials concerning design and protection of minors' rights that are being discussed. A detailed examination of how clinical trials with the participation of children are conducted today is provided. Special attention is paid to the use of "off-label" drugs in clinical practice. The authors predict further progress in creating favorable conditions for the participation of children in clinical trials and provide practical advice for achieving it.

Keywords: clinical trials involving minors, ethical review, pediatrics, experimentation, legislative regulation of clinical trials

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КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ С УЧАСТИЕМ ДЕТЕЙ: РОЛЬ ЭТИЧЕСКОЙ ЭКСПЕРТИЗЫ

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Статья посвящена роли этической экспертизы в клинических исследованиях с участием детей. Изучается исторический аспект этической составляющей клинических исследований с участием детей. Анализируется законодательное регулирование клинических исследований с участием несовершеннолетних в России и за рубежом. Поскольку сегодня потребность в педиатрических исследованиях уже не является предметом разногласий, и обсуждается в основном оптимизация планирования и выполнения педиатрических исследований с точки зрения дизайна и охраны прав несовершеннолетних участников, в статье подробно рассматривается то, как клинические исследования с учатием детей проводятся сейчас. Особое внимание уделяется использованию препаратов «off-label» в клинической практике. Авторы прогнозируют дальнейший прогресс в создании благоприятных условий для участия детей в клинических исследованиях и дают практические советы для его достижения.

Ключевые слова: клинические исследования с участием детей, этическая экспертиза, педиатрия, эксперимент, законодательное регулирование клинических исследований

Вклад авторов: Теплова Н. В. — разработка концепции и дизайна, редактирование, утверждение окончательного варианта статьи для публикации, ответственность за надлежащее изложение вопросов, связанных с достоверностью данных, целостность всех частей. Грацианская А. Н. — сбор, анализ, интерпретация материала, написание, языковое оформление текста, соответствие научной терминологии. Костылева М. Н. — офрмирование списка литературы по порядку упоминания источников в тексте.

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Clinical trials involving children as subjects are still the matter attracting a great attention of the society, especially as far as the ethical aspect goes. As an experiment is an essential part of any science development, experimental work in medicine has always been there, involving patients of any age. Edward Jenner (1798) conducted one of the first recorded medical experiments where children of different age groups had smallpox vaccination [1]. In the 19th century, when pediatrics has already become a separate branch of medicine, children in hospitals and orphanages have become a good resource for experiments. This didn't provoke any indignation in the society considering standards and norms of those times related to biomedical trials.

HISTORY OF PEDIATRIC CLINICAL TRIALS

During the World War II, children underwent mutilating experiments of the Nazi, who were convicted by the world community at the Nuremberg trial [2]. The resulting Nuremberg Code (1947) was the first document with provisions of biomedical research ethics. It requires compulsory informed consent to participation in any scientific experiment from a potential subject [3]. Thus, if a child can't consent to participation due to the limited legal capacity, involvement of children into biomedical trials was actually forbidden and the society had a deeply negative attitude to experiments involving children. However, until the 1960s

of the XX century, pediatric trials continued without any regulation.

In 1964, the World Medical Association developed and implemented the Nuremberg Code successor document, the Declaration of HelsinkiThe Declaration of Helsinki admits that clinical trials involving minors can be conducted in case when consent of parents or legally authorized representatives is provided [4].

Thus, in recent past, children were treated as a socially vulnerable group but at the same time pediatric clinical trials were understood necessary. Complexity of research pediatric activity, long-term lack of support at the state level and disinterest of pharmacological companies in pediatric trials caused a global shortage (or lack in some diseases) of registered (approved) pediatric dosage forms and the widely discussed issue of off-label (not according to the instruction) use of drugs among children [5]. By the close of the XX and at the dawn of the XXI century, international and national documents that regulate pediatric trials began to appear even in developed countries.

LEGISLATIVE REGULATION OF CLINICAL PEDIATRIC TRIALS

Guideline for Good Clinical Practice of the International Conference (Council since 2015) on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has evolved since 1996. In 2001, ICH GCP E11 Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population was developed [6]. The guideline determined basic provisions of drug development for children and approaches to safe, effective and ethically acceptable trials of drugs involving minors.

By 2007, the work related to implementation of ICH GCP E11 guideline provisions into regulatory documents of the European countries and USA consisted in the development of several important international and national documents for pediatric trials.

The EU pediatric legislation

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use [7];
- Regulation (EC) No 1902/2006, an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission [8].

The USA pediatric legislation

- Pediatric Research Equity Act (PREA) [9];
- Best Pharmaceuticals for Children Act (BPCA) [10];
- Title V of FDA Safety and Innovation Act (FDASIA) [11].

In the EU and USA, provisions of the mentioned regulatory documents create conditions, where pharmaceutical companies can/have to carry out trials of their medicines among children and decrease 'the-off-label-use' in children in the future. At present, we already have reporting FDA (Food and Drug Administration, USA) and EMA (European Medicines Agency, European Union) documents based on the results of over ten years of work during execution thereof. They show that the course of pediatric trial stimulation is successful, as basic prescribing information of hundreds of medicines has acquired pediatric indications [12, 13]. Though from a legal point of view, a medicine approved for use in children from other countries, but not registered for pediatric indications in the Russian Federation, remains off label in national pediatric practice, the actual data from open sources make the use of these medicines less risky for a patient in our country as well.

In the Russian Federation, there is no separate legislative document to regulate pediatric trials. That's why pharmaceutical companies decide whether they need to conduct pediatric trials to register children's indications, taking their own considerations into account. As state registration of a pediatric dosage form doesn't cause a significant growth of sales and is associated with certain technical difficulties and expenditures (clinical pediatric trials in Russia, state fee, etc.), a pediatric dosage form isn't most commonly registered even in its presence.

The significance of an ethical review is increased multiple times due to the lack of detailed legal regulation of many issues involving pediatric trials. Ethical standards of the trials with vulnerable patients are recorded in the Helsinki Declaration of the World Medical Association and ICH GCP Guideline.

'…19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research…'

Common legal requirements/limitations regarding inclusion of children in clinical trials are cited in Federal Law No. 61-FZ 'On Circulation of Medicines' [14], which takes all children as a vulnerable group, prohibits to treat orphaned children, children left without parental care and some other individuals (compulsory-duty servicemen, prisoners, law enforcement officials) as subjects of clinical trials.

Though GCP requirements to pediatric protocols do not differ from those for other groups of patients as far as relevance for obtaining valid results goes, it is erroneously to believe that a pediatric trial can use the same design as in adults [15]. It is known that a pediatric trial is often terminated prematurely due to a bad design (wrong determination of endpoints, non-applicability of a dosage form, unacceptability of some invasive procedures and/or their number, etc.) [16]. A prematurely terminated trial without significant results is not valuable for practical pediatrics. However, children already included into such an incomplete trial, have underwent the risk, and estimation of any trial perspectives can be an object of interest for an ethical review. Considering the protocol, experts of ethics committees compare the number and duration of planned visits, number of suggested procedures (particularly tender ones, such as vein puncture or intramuscular injection, or deep nasal or pharyngeal smears) and justify the necessity to estimate effectiveness and/or safety of the examined intervention.

For instance, when a locally acting treatment (i. e., throat spray) has been examined for 10 days, you can hardly explain the need in a biochemical blood assay sample, taken twice from a vein of 3–5-year-old children. Though the Ethics Committee doesn't estimate the scientific value of a trial, it determines whether the risk of inclusion of children into the trial is justified. Thus, in several cases, the committee can also pay attention to the scientific aspect of the trial. Ethics committees, that regularly deal with pediatric protocols, usually include a pediatrician and/or pediatric psychologist on a constant basis or can obtain an independent external opinion given by respective specialists.

From a legal point of view, a child is an individual from birth to adulthood (from 0 to 18 years old). Thus, another frequent matter of discussion is whether a clinical trial can be approved simultaneously in all age-specific subgroups or consistency

is better: approve inclusion first of 6–11-year-old children and then of 2–5-year-old children only after good results in 12–18-year-old adolescents have been obtained. This means that we need to shift to trials involving very small children only after data on effectiveness and safety for elder children have been collected. Followers of the subsequent approach are commonly not willing to approve simultaneous trials for all pediatric subgroups because they wish to protect those who are the most vulnerable, i. e., the youngest children, from risks of the trial until the examined intervention isn't proven effective and safe in elder children.

The approach is definitely reasonable. However, it is necessary to remember that delayed approval for inclusion of younger children remotes 'legalization' of practical use of the medicine among younger children. It is also necessary to take into account that it is more ethical and safe to use any medicine within a clinical trial (according to frequently checked/approved protocol by an experienced clinical investigator with exhaustive data about the examined medicine, with accompanying monitoring of the sponsor, with regular interim analysis results, under surveillance of the Ethics Committee and sometimes of a special Safety Committee), than to continue using the medicine off label in routine practice. The more serious an indication is, the more important it is to start trials in all age groups as early as possible. This is how the off-label period is reduced.

Apart from key features of a protocol design, a pediatric trial presents special requirements both to the process of gaining, and to the form of informed consent.

International documents and national legal instruments provide a unique solution stating that it is necessary to obtain consent of a potential subject's legal representative and consent of the minor (child) (Declaration of Helsinki, Federal Law No. 61-FZ). Unlike consent in a standard medical intervention, consent of a legal representative is always required when a child is included in a clinical trial. In the last case, the Russian legislation admits independent consent or refusal of medical intervention for adolescents elder than 15 years old [17].

In accordance with the legislation of the Russian Federation, legal representatives include parents, adopters, guardians and trustees [18]. However, only parents or adopters can sign consent to a child's participation in a clinical trial (No. 61-FZ). One parent's signature is usually enough only in case of no serious interventions when consent of both parents/adopters is deemed necessary. However, even in this case conditions when one parent is deemed to be 'substantially unavailable' must be determined.

The age when a child can take a conscious decision about participation/non-participation in a clinical trial is most frequently discussed. On the one hand, the principle of children's respect appeals to mobilize a child around taking important decisions about his/her own well-being as early as possible. On the other hand, can it be ethical to ask a small child to take such complicated decisions as participation in a clinical trial making him/her responsible for the consequences of refusal? There always exists a probability that a child can refuse to give consent due to mental peculiarities of his/her age because he/she is not able to understand how useful trial participation can be for his/her health or due to some other immediate considerations (acting against a doctor's/parent's will, because of poor health, fatigue, etc.). What will be the parental actions in this case? There exists a high probability that parents will make the child give such consent as they are aware of the advantages of trial participation. Then they will violate the basic principle of GCP about voluntary participation. A regulatory document determining the age when a child's consent is obligatory is currently lacking. As children of the same age can have different psychological and mental development features, every ethics committee decides upon the issue on an individual basis. For example, the issue can be solved by using the analogy of law [19] concerning the age of partial legal capacity, i. e., since 14 according to the civil code of the Russian Federation [20], or since the age of providing independent consent for/refusal of standard medical intervention set in 'The Fundamentals of the Legislation of the Russian Federation on the Protection of Citizens' Health' (15 years old) [21].

In the USA, many ethics committees (IRB — Institutional Review Board) suggest that a child's consent must be required since the age of 7 [22].

An ethics committee can discuss this issue and record the decision in the respective standard operation procedure (SOP) [23].

If the committee defines the age of compulsory consent in accordance with the abovementioned recommendations, the matter of including small children in a trial and their participation in the process of gaining informed consent is still open. Refusal of consent requirement for children who are too small to provide obligatory consent doesn't exclude the requirement to inform a child. Young children should be given information in an accessible form, for instance, as graphic novels or large-print texts with pictures depicting study procedures (MRI, blood sampling, examination by a doctor, etc.). The texts can also describe impressions experienced during the procedures (for example, 'an injection feels like an insect's bite', 'one needs to wear headphones while inside the MRI system as it is noisy', or 'you will be sleeping during gastroscopy and feel nothing', etc.). In this case, the data must not contain a consent request, but are intended for information only. Children are commonly fine with a doctor's recommendation to take part in a clinical trial, they like to have respectful conversations with medical investigators and the process of signing a consent form; later they will treat the research procedures in a responsible way.

CLINICAL PEDIATRIC TRIALS: MODERN TIMES

Discussing the issues of biomedical trials, we usually mean the clinical trials conducted by pharmaceutical companies to provide for state registration of their products (or other purposes), but where investigators perform only the function of collecting data as per the approved protocol. However, expertise of academic trials (including thesis research) has always been a separate challenge for Ethics Committees (particularly academic ones). In an academic trial, an investigator doesn't only collect data, but also acts as a sponsor, a documentation developer, a safety committee and a pharmacovigilance officer. A researcher is also responsible for the scientific aspect of an academic trial.

In our country, clinical trials have been arranged in accordance with international standards for over 20 years. An extensive cohort of experienced investigators, including a vast deal of supervisors of scientific divisions, Ph. D. thesis mentors and external Ph. D. students, has been formed in Russian centers (comprising the clinical basis of medical universities). Participation in international trials displays an example of a proper attitude to ethical and legal aspects of scientific activity. Paradoxical as it may sound, even experienced researchers are usually not aware that neither GCP rules, nor legislation of the Russian Federation make any differences between the requirements to trials conducting by pharmacological companies and initiative academic research involving human subjects [24].

However, it often happens that the goals of academic investigators are even more inventive than the ones of

pharmaceutical companies, both in planning, and conducting pediatric trials. Thesis papers of pediatricians sometimes correspond to the third or even second phase of pre-marketing trials (for instance, estimation of effectiveness and safety in children of a drug approved in adults or in a not previously examined dosage or with a new method of administration). Researchers usually ignore that trial participants must be insured in accordance with the law, that an approval from a regulator has to be obtained and many other conditions registered in regulatory documents. This is most typically of doctoral thesis papers, as traditionally collection of data for the papers must be almost completed by the moment of the topic approval. Local Ethics Committees of the universities monitor thesis works very rarely: they demand and obtain annual reports, serious adverse event reports, and approval of amendments to the protocol and informed consent.

It is obvious that a clinical trial planned in accordance with GCP standards and not contradicting the legislation of the Russian Federation requires long-term preparation, participation by a large team of diversified specialists and massive budget, delivery of documents to the Ministry of Health for revision (in some cases) and obtaining an approval for the trial. Can a university provide a proper quality of trial preparation as a sponsor, particularly in pediatrics? Can a university obtain a regulator's approval for the trials of their employees? Will manufacturers of medicines consent to conduct a trial of a medicine with preregistration signs at a university in accordance with the requirement of the Ministry of Health?

Theoretically, some of the abovementioned conditions can be fulfilled, but it is hard to do so from a practical point of view.

At first glance, both GCP guidelines and a legislative standard are roughly violated within academic science: patients are not protected, their rights are violated, data validity is not controlled, risky trials are conducted without a regulator's approval and LEC observations.

Fortunately, the reality is not that terrifying. The main problem is that in the majority of cases investigators determine their trial type (design) in a wrong way. They present it as a prospective, controlled, parallel-group and sometimes even randomized trial, though it is actually a retrospective, non-interventional, case-control trial. Even a trial of a new indication or effectiveness/safety in a not previously examined age group (for instance, in children) is actually a retrospective analysis of off-label use of a medicine in clinical practice. In pediatric clinics, off label indications are currently closely controlled, properly traced, and based on the algorithm from regulatory documents [25–29] after the necessity of such an indication has been discussed at a consilium or by a medical board and if a child's legal representative signed an informed consent form that had been compiled at a clinic.

Clinical pharmacologists are commonly these patients. Thus, a medicine is indicated in the interests of a patient (but not within a trial), a patient is insured via obligatory medical insurance, adverse events are traced using the pharmacovigilance system of a therapeutic institution, the primary documentation is maintained according to the regulatory requirements accepted in a clinic. When a trial design is determined in a correct way, in the majority of cases a trial subject is not a patient, but his/her case history. At the stage of a completed selection of the necessary number of medical records, submission of documents to the LEC is thoroughly acceptable from the point of an ethical review. In this case, the LEC must make sure that a patient's personal data are held confidential, and request a model of an individual registration card. Then it is not necessary to approve the informed consent form.

Thus, to conduct an ethical review of thesis research and other research and development trials, it's most important to provide a correct definition of a trial type (intervention or non-intervention) and design (retrospective or prospective). The majority of thesis works, which are disturbing for experts of the Local Ethics Committee (LEC), are actually non-interventional and retrospective. Due to the lack of risk to patients' health and/or impairment of patients' rights in retrospective trials, no monitoring of these trials is required by the LEC on a constant basis.

Unfortunately, postgraduates are not taught how to draft documents. That's why it is difficult for them to differentiate between a trial proper, which is subject to an ethical review, from routine medical practice. To change the situation for the better, increase the literacy of young researchers in methodology of clinical trials and acquire correct understanding of the value of an ethical review, the lecture course for postgraduates from Pirogov Russian National Research Medical University in 2021 included lectures about the basics of good clinical practice and methodology of clinical trials involving humans.

CONCLUSION

Now it is difficult to imagine that quite recently any discussion of pediatric trials started with questions 'Do we need clinical pediatric trials at all?', 'Can't we use the data from adults not to expose children to risk of participation in medical experiments?' [30, 31]. Currently, the need in pediatric trials is not a point for dispute. It is the issues of optimization of planning and conducting pediatric trials concerning design and protection of minors' rights that are being discussed.

Compliance with ethical principles stated in international documents acquires significance, which can't be overestimated in the lack of distinct legislative regulation. However, ethical standards, which are stricter than legal norms, are advisory in nature and make high demands on an investigator's personal moral attitudes and determination of members of the Ethics Committee. Growing experience of experts, slow development of regulatory documents reflecting different aspects of research activity in pediatrics, accessibility of information and technical simplicity of communication between all participants of the research process allow to expect further progress in creation of favorable conditions for participation of children in clinical trials.

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