# ETHICAL ASPECTS OF CLINICAL TRIALS OF BLOOD CLOTTING FACTORS IN CHILDREN WITH HEMOPHILIA

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The proportion of drugs for use in juvenile patients is much less than for the adult population. This is due both to the lack of specific drugs for a number of childhood diseases, and the need to conduct special clinical studies in different age groups to assess safety and efficacy parameters. When developing a program for clinical trials of an orphan drug, ethical aspects of the participation of underage patients are considered, taking into account the current international and Russian legislation. Obtaining the informed consent of a minor patient from one of the parents requires detailed prior information and the establishment of a trusting relationship before the participation of a minor patient in a clinical trial. The results of clinical and observational studies of orphan drugs on the example of moroctocog alfa in previously treated pediatric patients with hemophilia A in different age groups contribute to an increase in the arsenal of drugs for the treatment of orphan diseases in the pediatric population and determine the optimal conditions for the use of moroctocog alfa in different age groups.

**Key words:** clinical trials, observational trials, underage patients, informed consent, hemophilia A, moroctocog alfa

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# ЭТИЧЕСКИЕ АСПЕКТЫ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ ФАКТОРОВ СВЕРТЫВАНИЯ КРОВИ У ДЕТЕЙ С ГЕМОФИЛИЕЙ

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Доля лекарственных препаратов для применения у несовершеннолетних пациентов значительно меньше, чем для взрослой популяции. Это связано как с отсутствием специфических лекарственных препаратов при целом ряде детских заболеваний, так и с необходимостью проведения специальных клинических исследований в различных возрастных группах для оценки параметров безопасности и эффективности. При разработке программы клинических исследований орфанного препарата принимаются во внимание этические аспекты участия несовершеннолетних пациентов с учетом действующего международного и российского законодательства. Получение информированного согласия несовершеннолетнего пациента от одного из родителей требует подробного предварительного информирования и установления доверительных отношений до начала участия несовершеннолетнего пациента в клиническом исследовании. Результаты клинических и наблюдательных исследований орфанных препаратов на примере мороктокога альфа у ранее леченных пациентов детского возраста с гемофилией А в различных возрастных группах способствуют увеличению арсенала лекарственных средств для лечения орфанных заболеваний в детской популяции и определяют оптимальные условия применения мороктокога альфа в разных возрастных группах.

**Ключевые слова**: клинические исследования, наблюдательные исследования, несовершеннолетние пациенты, информированное согласие, гемофилия А, мороктоког альфа

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The proportion of drugs approved for use in juvenile patients is much less than for the adult population. On the one hand, this is due to the lack of specific drugs for a number of childhood diseases, and the need to conduct special clinical studies in a number of pediatric diseases [1]. On the other hand, development of new drugs for children with an inherited or acquired pathology requires a clinical study in different age groups with a detailed and complex assessment of safety and effectiveness parameters [2]. Planning, organization and conduction of clinical trials of new molecules in underage patients constitute a complex and time-consuming task. In the lack of indications to using the drug in children and results of clinical trials for the corresponding age group, underage patients with certain diseases are given medicinal preparations not registered for use in children of this age [3]. Shortage of medicinal agents approved for use in certain age groups of underage patients can urge pediatric specialists to run the risk by administering medicinal preparations according to vital indications not indicated for use in children of certain age. This risk is especially increased in children with pathology of an early age, and also in severe disorders, including orphan and rare diseases.

An approximate proportion of using non-registered drugs for underage patients varies from 45% on the inpatient basis to 10–20% on the outpatient basis [2]. The complexity of clinical trials in underage patients, especially the ones with an orphan pathology, is mainly associated with their difficult inclusion into a trial, limited number of patients with a certain pathology, and in some cases with necessary regular intravenous injections of the examined drug and frequent collection of blood biosamples to conduct a coagulologic trial [4].

Underage patients can participate in clinical trials only following proper expertise and approval of the protocol and clinical trial documentation by the central and local ethics committees. The committees protect interests of every underage participant of the clinical trial and guarantee observance of the required ethical and legal standards [5].

In accordance with the Russian legislation, children can be considered as potential patients of a clinical trial only if it is necessary to promote their health or prevent infectious diseases in childhood or if the purpose of the trial is to obtain data about the best dosage of a medicinal agent for pediatric treatment. Planning of the trial should be preceded by a clinical trial of a medicinal agent in underage patients. Cases when the examined medicinal agent is indicated for underage patients only are excluded [6].

The principal difficulties seen during clinical trials in underage patients can include the need in establishment of trust relationships with the parents of the underage patient and obtaining an informed consent from them, difficulties with inclusion of children in trials, low compliance of children and their parents, significant heterogeneity of pediatric population, particularly, of those with an orphan pathology, possible development of specific adverse reactions, difficulties in choosing the criteria assessing effectiveness and safety of the drug considering different types of clinical trial design in pediatrics and hematology [7].

## PECULIARITIES OF OBTAINING AN INFORMED CONSENT

Participation of children in a clinical trial of a medicinal agent is allowed only when a written consent of their biological and adoptive parents is provided. Thus, it is prohibited to conduct a clinical trial of a medicinal agent involving orphaned children and children deprived of parental care [6].

An information leaflet for parents of the underage, information leaflet for the underage patient (15 to 18 years of age) with the informed consent form must be approved in writing by the Ethics Council of the Ministry of Health of the Russian Federation and local ethics committees of research centers prior to the clinical trial [8].

A biological or adoptive parent of an underage child needs to examine the information leaflet for the parents of the underage patient prior to the clinical trial and provide a consent to participation in the trial by signing and dating the informed consent form of the leaflet. The written version of the informed consent form can be signed by one parent only. If those participating in the clinical trial (a parent or a child) disagree with each other, their inclusion into the trial is not possible.

In accordance with the Russian legislation, the minors, drug addicts elder than 16 years old and other underage elder than 15 years old can provide or withdraw an informed voluntary consent to a medical intervention, except for the cases of provision of medical aid according to urgent indications, in the presence of severe mental diseases, when committing socially dangerous acts and due to other reasons in accordance with parts 2 and 9 of article 20 of Federal Law No. 323-FZ [9].

Due to that, an underage patient aged 15 to 18 years along with one of his biological or adoptive parent must provide a consent to participation in the trial by signing and dating the respective informed consent form in the information leaflet for an underage patient aged 15 to 18 years. In this case a biological or adoptive parent of an underage patient aged 15 to 18 years must also read the information leaflet for the underage patient's parents and consent to participation in the trial by signing and dating the informed consent form.

Neither a researcher, nor other persons engaged in the trial must force or use other improper methods of exposure making an underage person and his biological or adoptive parents to participate or continue to participate in the trial. The researcher must inform the subject and his biological or adoptive parents of all significant aspects of the trial and provide them with the written information about the trial and positive conclusions of the Ethics Council and local ethics committees in the research center. Prior to signing an information leaflet, a researcher must provide underage patients and their biological or adoptive parents with enough time and possibility of obtaining more detailed information about the trial and taking a decision about a child's participation or refusal to participate. The patient and his biological or adoptive parents must obtain clear answers to all possible questions concerning the trial. Prior to the trial, the investigator who conducts an explanatory talk must sign and date the informed consent form in the information leaflet for the underage patient's parent and information leaflet for the underage patient along with the patient and one of his biological or adoptive parents, and provide the contact number.

During the explanatory talk, it must be explained as follows: purpose and procedures of the trial, patient's obligations, expected benefit, risk or inconvenience for a patient, other procedures or methods of treatment that can be available to the patients, apart from those allowed in the trial, and their potential benefit and risk, treatment that can be given to a patient if his or her health was inflicted during the trial. Important aspects include voluntary participation, and a possibility for an underage patient or biological or adoptive parents to refuse from participation or leave the trial at any moment without any sanctions or loss of agreed benefits. The underage patient and his biological or adoptive parents must timely read new information that can influence the wish of the patient and his/her biological or adoptive parent to continue participating in the

trial; have contact data of those persons who can be referred to for additional information about the trial and rights of patients in the trial; understand possible circumstances or reasons due to which participation in the trial can be terminated. During the explanatory talk, an underage patient and his or her biological or adoptive parents obtain data about the suggested duration of a patient's participation in the trial and approximate number of patients to be included into the trial [10].

## CONDUCTING CLINICAL TRIALS IN UNDERAGE PATIENTS WITH HEMOPHILIA

Clinical trials of effectiveness and safety of new medicinal preparations to treat hemophilia in children are characterized by significant peculiarities and regulated by certain requirements. Hemophilia is a hereditary hemorrhagic disorder occurring due to the lack of clotting factor VIII or IX in the blood [11, 12]. The majority of patients with hemophilia are represented by men. In many countries, the prevalence rate of hemophilia is 10–14 patients per 100,000 men. Meanwhile, the ratio of hemophilia A and hemophilia B is 4:1 or 1 case per 10,000–15,000 of newborn boys for hemophilia A and 1 case per 50,000 of those for hemophilia B [13, 14].

It must be noted that a number of patients with hemophilia in Russia has a tendency to increase during the last years. This is probably due to better detectability of a disease, increased longevity and quality of life in patients, migration to the regions where the specialized medical service is available. According to the World Federation of Hemophilia (WFH), 7,706 patients with hemophilia were registered in Russia with hemophilia A being diagnosed in 6,525 patients and hemophilia B in 1,181 patients [15].

In accordance with the international recommendations, clinical trials of recombinant and human plasma-derived coagulation factors VIII (FVIII) and IX (FIX) are conducted in different age groups. Thus, unlike the Russian legislation, the European Medical Agency (EMA) recommends to start a clinical trial of a new recombinant or human plasma-derived FVIII and FIX product in previously treated patients (PTP) with hemophilia of adults and children greater than 12 years of age due to alike pharmacokinetics [16, 17]. Obtaining results confirming effectiveness (E), safety (S) and comparable pharmacokinetic (PK) properties in 12 PTP with hemophilia A or B greater than 12 years of age during 50 days of administration (DA) is the basis for initiation of a similar trials in children who are 6 to 12 years of age. Obtaining the results of PK assessment, effectiveness in 12 PTP of 6 to 12 years of age, and 12 PTP of 0 to 6 years of age during 50 DA is sufficient to decide in favor of transition to clinical trials of effectiveness and safety of a new medicinal agent in previously not treated patients (PNTP) aged 0 and elder. Meanwhile, results of a clinical trial are required to include an indication into prescribing information for a new age, for instance, new factor FVIII products in 50 PTP with a severe form of hemophilia A in children both less and greater than 12 years of age, and at least 50 PTP who obtained a new factor FVIII product for up to 50 DA (fig.).

Registration of factor FVIII is followed by a post-registration trial in 200 PTP. 60 of them must be less than 12 years of age. In the post-registration period, treatment duration is up to 100 DA.

## STEP-WISE CLINICAL TRIALS OF RUSSIAN RECOMBINANT COAGULATION FACTORS IN UNDERAGE PATIENTS

The 'Development of pharmaceutical and medical industry' program for 2013–2020 has been implemented in the Russian Federation during the last 10 years. Its aim was to increase production and ensure availability of vital and most important Russian medicinal agents including drugs to treat hemophilia B [18, 19]. Implementation of the program in Russia resulted in proper development, industrial production and examination of a group of medicinal agents based on recombinant coagulation factors VII, VIII and IX to treat hemophilia A, hemophilia B and inhibitory hemophilia [20].

The hybrid program of clinical trials of Russian recombinant factor FVIII (moroctocog alfa, Octofactor) products combines the requirements of international and Russian regulatory documents concerning clinical trials in children with hemophilia A. The program was developed and implemented in accordance with EMA guidelines on clinical trials of factor FVIII, national requirements to clinical trials of medicinal agents, biological agents, principles of the World Medical Association's Declaration of Helsinki and principles of Good Clinical Practice of the Eurasian Economic Union [21, 22, 23].

The program of clinical trials of Russian recombinant factor FVIII products was implemented stage by stage in preregistration and post-registration periods for various age groups. Phase I clinical trial was carried out to examine pharmacokinetic properties, safety and tolerability of moroctocog alfa after its single use in 12 PTP who were 18 years of age and elder with severe and moderate hemophilia B [24, 25]. Phase II–III clinical trials were conducted to assess safety and effectiveness of moroctocog alfa in a multi-center, controlled, randomized, open-label, parallel-group clinical trial as compared with Octanate in 36 PTP with severe and moderate hemophilia A who were elder than 18 years of age [26, 27]. Based on the results of the clinical trials conducted in 2013, Octofactor (moroctocog alfa) was approved for human use in the Russian Federation [28]. A prospective, multi-center clinical trial of effectiveness and safety in 12 children who were 12 to 18 years of age with severe hemophilia A (phase IV) was conducted after registration of the drug to treat adult patients elder than 18 years of age.

Effectiveness of moroctocog alfa for prevention and on-demand therapy, and high safety in children with hemophilia A of 12 to 18 years of age was confirmed during the trial [29, 30].

A prospective, multi-center clinical trial of effectiveness and safety of moroctocog alfa in patients with severe hemophilia A elder than 18 years of age (phase IV) was also conducted after registration of the drug. It demonstrated preventive effectiveness and safety of factor FVIII products in 30 adult patients with severe hemophilia A [31].

Summed up data containing the results of clinical trials of moroctocog alfa in 50 PTP with hemophilia A elder than 18 years of age and children aged 12–18 years were the basis for initiating an open-label, prospective, non-comparative, multi-center, clinical trial of effectiveness, safety and pharmacokinetics of moroctocog alfa in 50 children with severe hemophilia A (phase III). Data of cohort I, which included 27 children 6 to 12 years of age, and cohort II with 6 children 2 to 6 years of age were analyzed separately. Patients were included into cohort II only when the clinical part of the trial was completed by all patients from cohort I and after intermediate analysis of effectiveness and safety. The obtained results show that moroctocog alfa was effective in both cohorts [32, 33].

In the post-registration period, two observational trials were conducted to collect additional information about safety and effectiveness of moroctocog alfa for patients with hemophilia A in real clinical practice. In a prospective, multi-center, open-label, observational trial of effectiveness and safety of moroctocog alfa in 237 patients with moderate and severe hemophilia A, data about preventive therapy results were collected during a year. Spontaneous bleedings occurring at

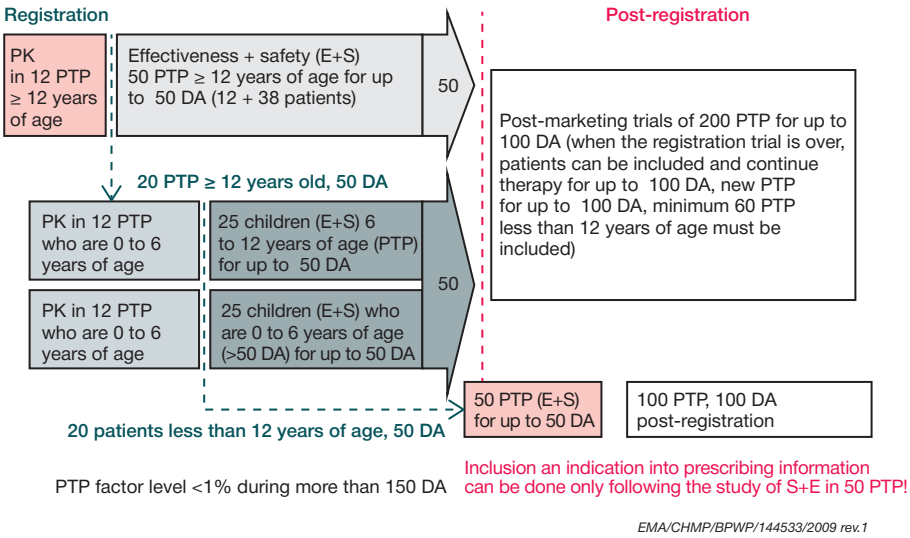


**Fig.** Sequence of clinical trials of new medicinal preparations of blood coagulation factor FVIII in different age groups [16]

2–3 days after administration of factor FVIII products were lacking in the majority of patients (61.7%). The average number of spontaneous hemorrhages occurring within 2–3 days after administration of the drug for a year for preventive purposes was 1.4±2.9 episodes per patient. During the trial, the drug demonstrated a high safety profile [34].

A prospective, multi-center, open-label, observational trial of effectiveness and safety of moroctocog alfa was additionally conducted in children with hemophilia A of 12 to 18 years of age in real-life clinical practice setting. During the trial the results of an examination and treatment of 24 PTP with hemophilia A were collected. They confirmed effectiveness of the agent in preventive treatment and its safety in the examined group of underage patients [35].

## CONCLUSION

Active use of modern technologies in the development of new medicinal agents for pediatric patients promotes expansion of therapeutic possibilities of various diseases by pediatric specialists and requires planning and conduction of necessary clinical trials.

Conduction of clinical trials of new medicinal agents in children with orphan diseases including hemophilia is still a complicated task due to difficulties of their inclusion, limited number of orphan patients, complex design of a trial with step-by-step inclusion in different age groups, need in a pharmacokinetic trial with a good venous access for frequent blood sampling and intravenous injections.

When developing the program of clinical trials of an orphan medicinal agent, ethical aspects of participation of the underage must be considered taking into account the current international and Russian legislation. The role of an underage patient's parents in the provision of an informed consent needs to be estimated properly as well. Thus, prior to participation of an underage in a clinical trial, they need to be well informed, all the issues have to be resolved, and trust relationships need to be established.

The accumulated results of clinical and observational trials in pediatric PTP with hemophilia A in different age groups enable to expand a number of drugs to treat orphan diseases in childhood, make treatment of hemophilia A more available for the underage patients and set optimal conditions of using moroctocog alfa in different age groups.

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