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НАУЧНЫЙ МЕЖДИСЦИПЛИНАРНЫЙ ЖУРНАЛ
ЯРОСЛАВСКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА
И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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ETHICAL ASPECTS OF CREATING CLINICAL GUIDELINES FOR PRACTITIONERS

Dreytser ED[1], Mudrova AV[1] ✉, Pavlov CS[2]

[1] The First Moscow State Medical University of the Ministry of Health of Russia (Sechenov University), Moscow, Russia

[2] Botkin City Clinical Hospital, Moscow, Russia

Clinical guidelines represent documents that contain structured information based on scientific evidence on prevention, diagnosis, treatment and rehabilitation, and regulate professional activities of the medical community. Starting from January 1, 2025, it is planned to switch to the mandatory use of clinical recommendations approved by the Ministry of Health of the Russian Federation, while the year of 2024 is an interim period for their application. However, various methodological and ethical issues arise while developing and discussing clinical recommendations. They include a conflict of interests of the authors, as well as aspects of its disclosure and settlement, accessibility of clinical recommendations for patients, as well as the discrepancy between the provisions of the recommendations and their evidence base such as results of systematic reviews and meta-analyses. Resolution of these problems will significantly improve the quality of clinical recommendations, and increase patient awareness of diseases and treatment approaches. This review analyzes a wide range of methodological problems related to the development of clinical recommendations, examines regulatory acts and ethical principles issued by government agencies, professional communities and international organizations, and makes suggestions to reduce the level of bias and, as a result, to increase the degree of evidence of clinical recommendations.

Key words: clinical recommendations, systematic review, meta-analysis, conflict of interest, systematic error, Cochrane

Author contribution: Dreytser ED — search and analysis of literature, writing the text of the article; Mudrova AV — search and analysis of literature, writing the text of the article; Pavlov CS — development of the basic concept of the study, writing the text of the article, editing the text of the article.

✉ **Correspondence should be addressed:** Anastasia V Mudrova
Svetlogorsky proezd, 5, sq. 58, Moscow, 125476, Russia; moodrova.a@yandex.ru

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ЭТИЧЕСКИЕ АСПЕКТЫ СОЗДАНИЯ КЛИНИЧЕСКИХ РЕКОМЕНДАЦИЙ ДЛЯ ПРАКТИКУЮЩИХ ВРАЧЕЙ

Е. Д. Дрейцер[1], А. В. Мудрова[1] ✉, Ч. С. Павлов[2]

[1] Первый МГМУ им. И. М. Сеченова Минздрава России (Сеченовский Университет), Москва, Россия

[2] Городская клиническая больница им. С. П. Боткина ДЗМ, Москва, Россия

Клинические рекомендации представляют собой документы, которые содержат базирующуюся на научных доказательствах структурированную информацию по вопросам профилактики, диагностики, лечения и реабилитации и регламентируют профессиональную деятельность врачебного сообщества. С 1 января 2025 года планируется переход на обязательное использование клинических рекомендаций, одобренных Министерством здравоохранения Российской Федерации, в то время, как 2024 год является промежуточным периодом их применения. Однако при разработке и обсуждении клинических рекомендаций возникают различные методологические и этические проблемы. Среди них можно выделить конфликт интересов авторов, а также аспекты его разглашения и урегулирования, вопрос доступности клинических рекомендаций для пациентов, а также несоответствие между положениями рекомендаций и их доказательной базой — результатами систематических обзоров и метаанализов. Урегулирование перечисленных проблем значительно повысит качество клинических рекомендаций, а также увеличит осведомленность пациентов о заболеваниях и подходах к лечению. В данном обзоре приводится анализ широкого спектра методологических проблем, связанных с разработкой клинических рекомендаций, рассматриваются нормативно-правовые акты и этические принципы, изданные государственными органами, профессиональными сообществами и международными организациями, и высказываются предложения для снижения уровня предвзятости и, как следствие, повышения степени доказательности клинических рекомендаций.

Ключевые слова: клинические рекомендации, систематический обзор, метаанализ, конфликт интересов, систематическая ошибка, Cochrane

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✉ **Для корреспонденции:** Анастасия Васильевна Мудрова
Светлогорский проезд, д. 5, кв. 58, г. Москва, 125476, Россия; moodrova.a@yandex.ru

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Clinical recommendations are documents regulating the professional activity of a doctor and containing structured information based on scientific evidence on prevention, diagnosis, treatment and rehabilitation, including patient management protocols (treatment protocols), medical intervention options and a described sequence of actions of a medical professional taking into account the course of the disease, the presence of complications and concomitant diseases, and as well as other factors affecting the results of medical care. Starting from January 1, 2025, it is planned to switch to the mandatory use of clinical recommendations approved by the Ministry of Health of the Russian Federation [1]. The year of 2024 is a transitional period for the application of clinical recommendations [2].

In the process of developing and discussing clinical recommendations by experts, a number of methodological and ethical problems arise. They include a conflict of interests of the authors, availability of clinical recommendations to patients, discrepancy between the clinical recommendations and the initial evidence base, results and conclusions of systematic

reviews, which belong to the most evidence-based method of analyzing scientific data. This paper examines a wide range of methodological problems related to the creation of clinical recommendations.

MATERIALS AND METHODS

The available literature devoted to the creation of clinical recommendations and the methodological and ethical problems that arise in this case is analyzed. We also reviewed the regulatory and ethical framework governing the development and implementation of clinical guidelines. These include relevant laws, regulations, guidelines and ethical principles issued by government agencies, professional communities and international organizations. Key documents regulating this area include materials published by the World Health Organization (WHO), the Association of American Medical Colleges (AAMC), the NICE Advisory Committee and the Clinical Guidelines Committee of the American College of Physicians of the American College of Physicians (ACP) [3–5]. For clarity, we used the findings and data from systematic reviews developed by the Cochrane Community Hepatobiliary Group (CHBG) included in a number of international clinical recommendations.

Below we provide a detailed analysis of regulatory legal acts and case studies on the ethical issues of forming clinical recommendations, and make suggestions on how to reduce the level of bias. Potential systematic errors in the selected literature and research topics represent a limitation of our research.

RESULTS AND DISCUSSION

Ethical aspects of writing systematic reviews

The review examines the ethical aspects of writing systematic reviews taking Cochrane research as an example. Cochrane systematic reviews are rightfully recognized as research of the highest quality, which are resistant to bias due to a strict standardized methodology.

Conflict of interest statement

A conflict of interest is a declaration by the author, which contains provisions reflecting a personal direct or indirect interest that affects or potentially has an impact on the proper, objective and impartial performance of official duties. By strength, conflicts of interest are divided into conflicts of high, moderate and low strength, they are divided into active and inactive ones by activity, and into financial and intellectual ones by type [4]. Conflict of interest is one of the main ethical aspects affecting the content of clinical recommendations. To identify a conflict of interest, it is necessary to disclose all possible conflicts of interest.

Members of the Cochrane Community are required to declare any potential conflicts of interest annually and/or when circumstances change. The members of the Management Board declare all potential conflicts of interest over the previous ten years. For other positions, the corresponding period is three years [6]. A conflict of interest is declared with the help of questionnaires. They are compiles and filled in using the Convey Global Disclosure System, created by the Association of American Medical Colleges (AAMC).

The main questions of the questionnaire relate to accepting offers from commercial organizations with a financial interest in the field of research by the applicant/his spouse/partner/relative, owning shares or parts of the shares in a commercial organization with a financial interest in the field of research, owning planned, issued or pending patents for products related to the field of research.

Accessibility of information for patients

An important ethical aspect of the compilation of systematic reviews includes accessibility of information to patients. To do this, a patient-oriented summary is created for each review. A team of volunteers is engaged in translating it from English into other languages [7]. This form makes it possible to inform patients about the methods of treatment and diagnosis of their diseases, which increases the rate of awareness [8].

Ethical aspects of making clinical recommendations

An algorithm for resolving conflicts of interest in the preparation of clinical recommendations

The main ethical principles of creating clinical recommendations are transparency, proportionality, and impartiality. Transparency means that all information about participants and solutions for managing conflicts of interest is freely available. According to the principle of proportionality, the strategy of interest conflict management should be strengthened as their severity increases. Conflict of interest should be assessed in an impartial manner [4].

The Clinical Guidelines Committee of the American College of Physicians recommends the following algorithm for dealing with conflicts of interest. Authors of clinical recommendations fill in questionnaires about the presence of interests before starting work on clinical recommendations, during which the authors are required to declare new conflicts of interest. It is also necessary to fill in a questionnaire on conflicts of interest a year after writing clinical recommendations. A panel of experts evaluates conflicts of interest and divides them into groups depending on their strength.

Low-level conflicts of interest include any inactive high-level conflict (for example, the author was a member of the advisory board of a pharmaceutical company, but resigned last year), any intellectual interest, which is only relatively related to a clinical topic (for example, the author participates in writing a weight loss manual and during the previous three years participated in a study evaluating the effect of various diets on cardiovascular diseases). In this case, the author can freely participate in writing clinical recommendations.

Moderate conflicts of interest include intellectual interest, which can lead to a cognitive bias (for example, the author involved in the creation of clinical recommendations for blood pressure control has been researching drugs for hypertension for the previous 3 years), relationships with organizations that can profit from cooperation with recommendations, but are not interested in clinical conclusions of the recommendations (for example, patent interest in software related to clinical decision-making). Experts with medium-strength conflicts of interest can participate in the discussion, but they are not entitled to be authors of recommendations and participate in voting.

Any active relationship (financial or other) with high-risk organizations is considered a strong conflict of interest (for example, an expert is currently a member of the advisory board of a pharmaceutical company). If the expert is ready to eliminate the conflict of interest, then he can be allowed to develop a clinical recommendation. If the expert is unable or unwilling to reduce the severity of the conflict of interest, he is excluded from participation [4].

Inconsistency of the provisions of clinical recommendations with the results of systematic reviews

The provisions of clinical recommendations may quite often not correspond to the results of systematic reviews. Participants of the Cochrane Community hepatobiliary group conducted a study comparing data from 7 systematic reviews prepared by the Cochrane Community and 62 provisions of 9 clinical recommendations of AASLD, EASL, NICE and BSG professional communities. The following topics were included in the study: ascites, hepatorenal syndrome, prevention and treatment of spontaneous bacterial peritonitis, primary and secondary prevention and treatment of bleeding from varicose veins of the esophagus. The consistency between the conclusions of the authors of the recommendations and the independent assessment was 0.145 (95% CI: 0.077 to 0.256), therefore, disagreement was found in 85.5% of the statements of the recommendations and the initial data of systematic reviews [9]. Thus, the strength of the recommendations was overestimated, which suggests the need to introduce mandatory disclosure of conflicts of interest for compilers of clinical recommendations.

Not all international and Russian professional communities adhere to the policy of disclosing conflicts of interest. Some experts prefer the results of their own research when making clinical recommendations, and this is an important ethical issue. This ethical problem can be solved by introducing a mandatory questionnaire on the alleged conflicts of interest.

The skill of searching for and evaluating systematic errors is currently not a criterion for selecting compilers of clinical recommendations, which may also lead to a selective choice of the provisions of clinical recommendations. To resolve this contradiction, it is possible to introduce mandatory testing and determine the qualifications of potential authors of clinical recommendations. It is also possible to use systematic error assessment tools such as GRADE and AMSTAR 2 when evaluating systematic errors in clinical recommendations. GRADE (Grading of Recommendations, Assessment, Development, and Evaluations). GRADE is a transparent system for the development and presentation of summaries of evidence, through which a systematic approach to making recommendations for clinical practice is possible. This is the most widely used tool for evaluating the quality of evidence and making recommendations: GRADE is officially supported by more than 100 organizations around the world, including Cochrane [10]. AMSTAR 2 is a tool for determining the methodological quality of systematic reviews of intervention studies [11].

Clinical recommendations for patients

An equally important ethical task is to create information about clinical recommendations accessible to patients, following the example of summaries created by the Cochrane Community, or a free version of UpToDate for patients and their relatives [7, 12]. Thanks to adapted clinical guidelines, it is possible to raise awareness about the prevention and treatment of their diseases, which can help patients protect their rights when receiving medical care. It is advisable to ensure access to paid Internet services that allow to look through the abbreviated versions of clinical recommendations, for example, Reclin for Russian doctors and the Up-to-Date English-language resource [11, 12]. Such platforms are aimed at practitioners who do not have enough time to familiarize themselves with the full version of clinical recommendations. It is possible to solve the problem of insufficient patient awareness by creating similar free resources for a wide audience.

CONCLUSIONS

A clinician does not have the time and methodological skills to analyze systematic errors in clinical recommendations. Experts who compile the recommendations need to conduct a thorough methodological analysis of systematic errors, since the conclusions of the practical guidelines directly affect the process of making a medical decision. The international experience in making recommendations for clinical practice indicates that a number of conclusions of the recommendations do not reflect the results of systematic reviews, whereas overestimation of the strength of the evidence base has a negative impact on the health of patients and the healthcare system. It is advisable to include a patient-oriented section in the clinical recommendations so that they can get clear, accessible and comprehensive information about their diagnosis and save the time resource of outpatient doctors.

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COMPARATIVE ANALYSIS OF THE ADAPTABILITY OF COVID-19 PANDEMIC CLINICAL TRIAL PROTOCOLS BY SEVERAL SPONSORS

Khokhlov AL, Eleskina AA ✉, Belchik LM

Yaroslavl State Medical University, Yaroslavl, Russia

The pandemic caused by the SARS-CoV-2 virus has put a huge strain on health systems around the world. Clinical trials of new drugs were also influenced by the pandemic, during which Sponsors came across a number of problems, including ensuring patient safety and maintaining the ability to obtain reliable data in the course of ongoing research. The purpose of this study was to compare the protocols of clinical trials of two Sponsors, approved by the Russian health authorities for three years, from 2017 to 2019, by their adaptability to the SARS-CoV-2 virus pandemic. 23 protocols and 51 amendments were studied in total. The amendments published in 2020 by both Sponsors underwent a comparative analysis to determine the degree of their influence by the pandemic. Statistical processing of the results was carried out using the correlation analysis. Conclusions were drawn about the Sponsors' approach to clinical trial planning and establishing the safety margin of clinical trial protocols.

Keywords: COVID-19, clinical trials, clinical trial protocol, clinical trial protocol amendment

Contribution of the authors: Khokhlov AL — editing, final approval of the manuscript; Eleskina AA — development of the idea and carrying out the work, analysis and interpretation of the results, processing of literature, writing the text; Belchik LM — writing the text, editing.

✉ **Correspondence should be addressed:** Anastasia A. Elsekina
Revolyutsionnaya str., 5, Yaroslavl, 150000, Russia; anastasia.eleskina@yandex.ru

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ АДАПТИВНОСТИ ПРОТОКОЛОВ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ К ПАНДЕМИИ COVID-19 НЕСКОЛЬКИХ СПОНСОРОВ

А. Л. Хохлов, А. А. Елескина ✉, Л. М. Бельчик

Ярославский государственный медицинский университет, Ярославль, Россия

Пандемия, вызванная вирусом SARS-CoV-2, создала огромную нагрузку на системы здравоохранения по всему миру. Под этим влиянием оказались и клинические исследования новых лекарственных препаратов, в течение которых спонсоры столкнулись с рядом проблем, в том числе с обеспечением безопасности пациентов и сохранением возможности получения достоверных данных в ходе текущих исследований. Целью данного исследования было сравнение протоколов клинических исследований двух спонсоров на их адаптивность к пандемии вируса SARS-CoV-2, утвержденных органами здравоохранения России в течение трех лет, с 2017 по 2019 г. включительно. Всего было изучено 23 протокола и 51 поправка. Поправки, опубликованные в 2020 г. обоими спонсорами, подверглись сравнительному анализу для определения степени влияния на них пандемической ситуации. Статистическая обработка результатов проводилась с использованием корреляционного анализа. Были сделаны выводы о подходе спонсоров к планированию клинических исследований и о запасе прочности протоколов клинических исследований.

Ключевые слова: COVID-19, клинические исследования, протокол клинического исследования, поправка к протоколу клинического исследования

Вклад авторов: А. Л. Хохлов — редактирование, финальное утверждение рукописи; А. А. Елескина — разработка идеи и проведение работы, анализ и интерпретация результатов, обработка литературы, написание текста; Л. М. Бельчик — написание текста, редактирование.

✉ **Для корреспонденции:** Анастасия Александровна Елескина
Революционная ул., д. 5, г. Ярославль, 150000, Россия; anastasia.eleskina@yandex.ru

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Many spheres of human life such as society, trade, economy, and environment were influenced by the SARS-CoV-2 pandemic but it was the global health system that experienced the maximum burden. This also affected the conduct of clinical trials of new drugs, as Sponsors, centers and researchers faced a number of serious problems.

They primarily concerned the possible risk of the virus spreading among participants in clinical trials, other patients, and medical professionals [1]. Due to government restrictions on the movement and border closures, which caused interruptions in the supply of equipment and investigational medicines, some studies were stopped or recruitment of new patients was slowed down [2,3], and a quarantine was enforced or centers were closed as they focused on dealing with COVID-19 infection [4,5].

The impact of the above problems on current clinical trials can be considered inevitable, since health systems and societies as a whole were not ready to cope with such a situation, and therefore global health authorities had to react promptly to the problems encountered during the research.

In several countries, regulatory authorities were forced to slow down and even stop issuing permits for new clinical trials, for example, the EU guidelines on conducting clinical trials during the COVID-19 pandemic recommended to critically evaluate the start of new studies if they were not aimed at testing new drugs for the treatment of COVID-19 [6].

The Russian health authority also introduced some changes. According to the data, in 2020 [7] the average period for obtaining permission to amend protocols increased from 48 to 65 days compared to 2019. Also, the period for obtaining permits for conducting clinical trials, import of medicines and import/export of biological samples increased from 87 to 103 days, from 15 to 17 days and from 20 to 22 days, respectively. At the same time, permits to conduct the trials for COVID-19

treatment were issued on an accelerated basis, but COVID-19 research occupied the 3rd place only in terms of the number of permits issued for clinical trials.

In this critical situation, the U. S. Food and Drug Administration (FDA) has also published new guidelines for conducting clinical trials [8].

At the same time, the pandemic has driven the regulatory authorities towards introducing elements of decentralized research. These are studies in which some or all of the clinical trial activities take place in a non-traditional location, such as home of the study participant, a local medical facility, or the nearest laboratory. It also implies the use of digital technologies such as electronic consent, applications, portable devices, patient-reported results, and telemedicine [9].

It is important to note that the primary tasks for Sponsors and health authorities were to ensure the safety of test participants during ongoing clinical trials [10,11] and to preserve the possibility of obtaining reliable data and compliance with all measures prescribed by the protocol. In this regard, pharmaceutical companies were forced to solve the problem of continued use of the studied drugs for the included participants and the need to change the methods and place of monitoring during ongoing studies.

Thus, at the same time, home visits were introduced to patients (to collect laboratory tests and infusions of investigational drugs), direct delivery of educational materials and medicines to participants, video and telephone assessment (for example, to check the patient's safety and current health status, to report test results), and remote patient monitoring by the Sponsor [12,13].

Thus, the problem of compliance with the protocol-specified procedures such as systematic administration of the investigational drug, adherence to prescribed protocols, evaluation of treatment effectiveness, laboratory procedures and analyses, as well as adequate monitoring by Sponsors has been solved. And this, in turn, could affect reliability and interpretation of the data obtained during the research [14, 15].

However, the Sponsors were required to describe all new changes affecting the safety and well-being of patients, as well as to provide clear instructions to research teams for each individual study by issuing amendments to clinical trial protocols. As it is known, an additional purpose of issuing these amendments is to prevent financial losses by closing expensive trials [16].

At the same time, amendments to clinical trial protocols are common practice and their release is due to a number of reasons, for example, the introduction of new standards of care; changes related to medicines that were approved for use before and during a clinical trial; availability of new safety data; requests from regulatory authorities and other supervisory organizations. Also, the reasons for amending the protocol may be amended criteria for inclusion of patients due to a change in the research strategy and difficulties in recruiting patients [17,18].

The study [19] analyzed the impact of the COVID-19 pandemic on changes in clinical trial protocols, according to which 14 protocol amendments were issued in 2020, at the height of the pandemic. Only one of them was related to the COVID-19 pandemic and released at the initiative of the Sponsor, which shows a high level of concern for patient safety. The remaining 13 amendments were about the routine changes during the study. Therefore, it can be concluded that, in general, the company has a comprehensive approach to how clinical trials can be planned, since protocols have a margin of safety. That is why the pandemic did not affect the increase in the number of amendments issued. An analysis of the amendments of the aforementioned Sponsor showed that its protocols had a margin of safety, however, we could not apply this statement to all Sponsors of clinical trials. In this regard, the already studied protocols of Sponsor I and the yet unexplored protocols of clinical trials of Sponsor II were compared to find out how adaptable the protocols are in response to the SARS-CoV-2 virus pandemic.

MATERIALS AND METHODS

Amendments to the research protocols of two Sponsors, who were granted permits by the Ministry of Health of the Russian Federation to conduct clinical trials for 3 years (2017–2019) were analyzed.

During this period, Sponsor I of the Ministry of Health of the Russian Federation approved 27 clinical trials, 5 of which were subsequently given to contract organizations to conduct clinical trials. In 2 of 22 studies, there were no amendments to the protocol, so they were not included in the analysis.

Sponsor II received permits to conduct research only in 2019, no approvals were received for 2017 and 2018. Thus, 3 clinical trials and 12 amendments hereto were reviewed.

THE RESULTS OF THE STUDY

Sponsor I

The largest number of adjustments to the CI protocols were issued in 2020, namely, there were 14 (36%) of them. There were fewer (13 (33%)) amendments in 2019, 9 (23%) in 2018, whereas the minimum number (3 (8%)) was recorded in 2017 (fig.1).

In 2020, 14 amendments were issued, which is the largest number within the all the analyzed years, with 5 of the 14 being associated with requests from health authorities. At the same time, only one amendment was issued in response to the ongoing COVID-19 pandemic as it was difficult for patients to make visits to the center and receive the investigational drug. Accordingly, the schedule of visits was adjusted and the possibility of delivering the drug to patient's home was provided. One adjustment was associated with the identified risk of hepatitis B reactivation, and another one with the addition of drugs as recommended concomitant therapy for patients participating in the study. The reasons for the release of three subsequent amendments are as follows: a change in the dosage of the drug used in the study, introduction of additional parameters for the distribution of patients and clarification of general information about the study. The other two adjustments relate to a change in protocol procedures. At the same time, different sections of all issued amendments contained adjustments in response to the ongoing pandemic in order to ensure patient safety and preserve the possibility of obtaining reliable data in the course of research. For example, it was allowed to include patients who changed studies and

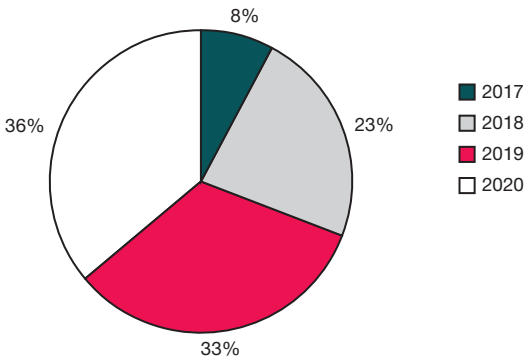

Figure 1. Distribution of Sponsor I's amendment output by year

could not complete the end-of-treatment visit as part of the previous study. Additionally, the possibility of delivering the drug from the centers to the home of CI participants was added.

Sponsor II

The largest number of edits was published in 2019. It slightly exceeds a half of the total (58%). Only two (18%) amendments, two (18%) amendments and one more amendment were published in 2020 (18%), 2021 (18%) and 2022 (9%) respectively. It should be noted that no amendments were issued in 2017 and 2018, since no single study was launched by Sponsor II in these years (fig.2).

In 2020, the first amendment was issued in connection with an update of security data and a change in visit procedures. The second amendment was published due to data clarification and editorial changes, that is, it was typical for emerging changes during the course of a clinical trial. Note that none of these amendments were related to the COVID-19 pandemic, but all of them were associated with the routine practice of conducting a clinical trial.

Nevertheless, in addition to routine changes to the first amendment under consideration, changes related to the pandemic were nevertheless included, namely, information on the need to ensure patient safety, compliance with the therapy regime, and admission of alternative methods of conducting visits (telephone contact, virtual visit, conducting some visits at home, home delivery of medicines, postponement of the visit, collection of biological samples and conducting procedures at home), which will not be considered deviations from the protocol and preserve the integrity of the study itself, will be added to the section on deviations from the protocol. Within the framework of the same protocol, the criteria for significant deviations from the protocol were clarified. At the same time, due to the situation caused by the SARS-CoV-2 virus, other paragraphs of the protocol text within the amendment did not contain any additional changes. In another study, which underwent changes in 2020, information about the impossibility of including a patient in the study or excluding an already treated patient if he has a positive rapid test for the SARS-CoV-2 antibodies was added to the 'Exclusion/non-inclusion criteria' section.

Accordingly, an express coronavirus test was included in the list of procedures at the screening visit and in the list of necessary laboratory tests, and the parameters for including patients in the study were adjusted. Centralized and/or remote monitoring was provided, ensuring the proper quality of the clinical trial and respecting the rights of the patient.

At the same time, no adjustments regarding changes in the types of visits for patients or the introduction of elements of decentralized research, the use of which would not be considered a deviation from the protocol, were added to this protocol as in the previously considered amendment.

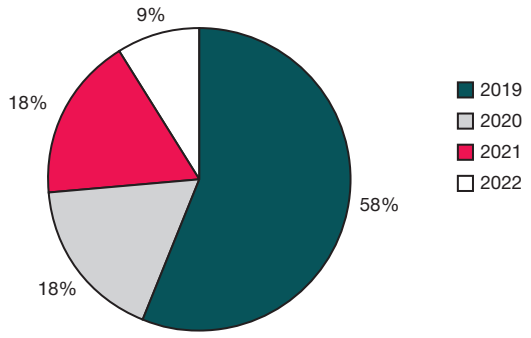

Figure 2. Distribution of Sponsor II's amendment output by years

DISCUSSION OF THE RESULTS

Sponsor I published 14 amendments in 2020, while only one amendment was issued in response to the ongoing COVID-19 pandemic as it was difficult for patients to make visits to the center, and receive a drug, accordingly. All other edits were related to regular updates of data and information during research.

In 2020, Sponsor II released only 2 routine corrections in 2 different studies. It is worth noting that the number of adjustments issued during the year was very different compared to Sponsor I, however, this is due to the number of conducted trials.

CONCLUSIONS

Thus, it can be concluded that Sponsor I demonstrates a comprehensive approach to how clinical trials can be planned, since the protocols have a margin of safety and do not require surgical intervention for adjustments during emergencies. It is only necessary to include any relevant additions and clarifications in the protocols for the research team. It is safe to say that Sponsor I reacted promptly to the ambiguous global situation by adapting the current tests to the decentralized research.

The situation with Sponsor II is ambiguous, since, on the one hand, the number of amendments in this year is minimal, however, the changes that we see in the issued amendments do not fully guarantee that these protocols have a margin of safety and will be able to provide reliable data. This is due to the fact that one amendment provided for remote visits and home delivery of the drug for patient safety, but the possibility of remote data monitoring was not included. Also, the situation with patients who are being treated already, who are likely to be diagnosed with a viral disease, and its impact on their health status, as well as on obtaining data, was not thought out.

In the Second Amendment, changes in response to the pandemic situation had a more thoughtful approach to patient health safety. This was due to the inability to include the patient in the study or exclude an already treated patient if he had a positive rapid test for antibodies to the SARS-CoV-2 virus. At the same time, this amendment did not include the variability in the methods of conducting routine visits for patients, while remote monitoring visits for the Sponsor were allowed.

Thus, Sponsor II partially implemented elements of decentralized research, which, in one case, did not fully ensure patient safety, without addressing the problem of the quality of the data obtained. In another case, the safety of the treated patients was ensured to a greater extent, as well as obtaining reliable information during the study.

It can be concluded that the quality of the data obtained by Sponsor II during the research is questioned due to the unreliability and lack of thought of the issued amendments to the protocols. These protocols are not adaptive in emergency situations, both from the point of view of a patient's safety and from the point of view of the possibility of reliable data obtained during research and their interpretation. Moreover, the Sponsor was unable to adapt the research to a decentralized format in an emergency situation. This analysis showed that Sponsors of clinical trials should pay attention to a more thoughtful approach to writing clinical trial protocols to ensure a wider margin of safety and their adaptability to the constantly changing reality in which clinical trials are conducted. Regulatory authorities in the health sector should also draw the attention of Sponsors to this problem while approving research on the territory of a particular country.

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ETHICAL AND SOCIAL ASPECTS OF TEENAGE PREGNANCY

Kurmangaleeva AYu[1] ✉, Sibirskaya EV[1,2]

[1] Morozovskaya Children's City Clinical Hospital of Moscow, Moscow, Russia

[2] Russian Children's Clinical Hospital, a branch of N. I. Pirogov Russian National Research Medical University, Moscow, Russia

Teen pregnancy remains one of the key social issues that deeply affects not only the life of a young mother and her child but their inner circle and society as well. In spite of multiple efforts to reduce its prevalence rate, teen pregnancy is still a pressing issue in many countries. Currently, there are several key problems that can result in an increased risk of teen pregnancy. They include an early beginning of sexual activity, history of sexual abuse, low social and economic status, lack of parental care and support, cultural and family behavioral models, use of psychoactive substances, poor academic performance and expulsion from school. In addition, the probability of a repeated teenage pregnancy is significantly increased, passing the problem on from one generation to another. This article is aimed at a comprehensive analysis of these factors and statistical data in order to better understand the problem of teenage pregnancy, assess its consequences for the health and well-being of those underaged and their children. Special attention is paid to the ethical and social aspects of teenage pregnancy.

Keywords: teenage pregnancy, social issues, sexual education, rights of minors, reproductive health of children and adolescents, public health

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Correspondence should be addressed: Aliya Yu. Kurmangaleeva
4-th Dobryninskiy pereulok bld. 1/9, Moscow, 119049, Russia; askarova-aliya@yandex.ru

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ЭТИЧЕСКИЕ И СОЦИАЛЬНЫЕ АСПЕКТЫ ПОДРОСТКОВОЙ БЕРЕМЕННОСТИ

А. Ю. Курмангалеева[1] ✉, Е. В. Сибирская[1,2]

[1] Морозовская детская городская клиническая больница г. Москвы, Москва, Россия

[2] Российская детская клиническая больница, филиал РНИМУ им. Н. И. Пирогова, Москва, Россия

Подростковая беременность остается одной из ключевых социальных проблем, оказывающих глубокое влияние не только на жизнь самой молодой мамы и ее ребенка, но и на близкое окружение и общество в целом. Несмотря на множественные усилия по снижению ее распространенности, подростковая беременность продолжает быть актуальной проблемой во многих странах мира. В настоящее время выделяют несколько ключевых факторов, которые могут способствовать повышенному риску возникновения подростковой беременности. Среди них — раннее начало половой жизни, анамнез сексуального насилия, низкий социально-экономический статус, недостаток родительского внимания и ухода, а также культурные и семейные модели поведения, употребление психоактивных веществ, плохая успеваемость и отчисление из школы. Кроме того, вероятность повторения сценария подростковой беременности в собственной жизни молодой мамы значительно возрастает при перекладывании проблемы из поколения в поколение. Данная статья направлена на всесторонний анализ указанных факторов и статистических данных с целью лучшего понимания проблемы подростковой беременности, оценки ее последствий для здоровья и благополучия несовершеннолетних и их детей. Особое внимание уделено этическим и социальным аспектам, связанным с подростковой беременностью.

Ключевые слова: подростковая беременность, социальные проблемы, половое воспитание, права несовершеннолетних, репродуктивное здоровье детей и подростков, общественное здравоохранение

Вклад авторов: А. Ю. Курмангалеева, Е. В. Сибирская — концепция и дизайн исследования; А. Ю. Курмангалеева — сбор, обработка материала и написание текста, Е. В. Сибирская, А. Ю. Курмангалеева — редактирование.

✉ **Для корреспонденции:** Алия Юнусовна Курмангалеева
4-й Добрынинский переулок, д. 1/9, г. Москва, 119049, Россия; askarova-aliya@yandex.ru

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In modern society, sexual relations among minors are perceived as something common without being condemned or receiving much attention from adults. However, despite the apparent normalization of early sexual contacts, the topic of personal hygiene and contraception in the framework of family education remains insufficiently covered, which often leads to negligence of these important aspects. Due to this trend, the cases of early sexual intercourse are on the rise making it a normal thing before marriage. However, the problem of teenage pregnancy continues to be relevant and arouses lively public interest[1, 2]. For example, only 40% of teenage mothers graduate from high school and less than 2% complete the college [3]. The purpose of this review is a comprehensive analysis of the factors affecting teenage pregnancy and an assessment of its consequences for the health and well-being of minors and their children.

MATERIALS AND METHODS

A literature review was conducted, including articles and reports from international organizations such as WHO and UNICEF. Statistical data, trends and risk factors of teenage pregnancy taken from national and international databases, including Rosstat and WHO, are analyzed. A quantitative analysis of data on fertility, abortions and the risks of teenage pregnancy was performed. The literature was searched for keywords such as 'teenage pregnancy', 'medical ethics' and 'legal aspects' limited by language (Russian and English) and document type.

The purpose of the article is a comprehensive analysis of the ethical and legal aspects of teenage pregnancy. The article is aimed at assessing the impact of teenage pregnancy on health and well-being of minors and their children, as well as

studying statistical data and influencing factors for a deep understanding of the problem and formation of an adequate legal framework for all stakeholders.

DISCUSSION

There was an increase in the birth rate among adolescents up to the 1990s, but subsequent years were marked by its decrease. This trend is closely related to the so-called contraceptive revolution. The basic changes occurred due to a significantly improved access to contraceptives. In the west, changes occurred in the 1960s and 70s, while in Russia it happened much later. In the USSR, there was no domestic production of hormonal contraceptives, and official medical policy was skeptical about their use due to possible side effects. In the decade of the 2010s, the teenage birth rate has begun to decline again. According to experts, it happened due to spread of smartphones, which made information about contraception much more accessible. Thus, access to information about methods of prevention has contributed to a decrease in the birth rate among adolescents both in Russia and western countries.

According to data obtained in 2019, the number of pregnancies among adolescents aged 15 to 19 in low- and middle-income countries is equal to approximately 21 million pregnancies per year [4]. Half of these pregnancies are unplanned, and 55% of these unplanned pregnancies end in abortions, many of which are criminal.

According to WHO, [5] the fertility rate among girls aged 15–19 years decreased from 64.5 cases per 1,000 girls to 42.5 cases per 1,000 girls in 2021.

According to UNICEF [6] and a meta-analysis of 217 publications [7] with a total of more than 9 million participants, it was revealed that one of eight girls under the age of 18 was sexually abused.

The number of births by maternal age and the order of birth in the Russian Federation in 2022 are presented in table 1.

The number of births by maternal age decreases every year. Thus, it amounted to 54,074 among those aged 15–17 years and 221,473 among those aged 18–19 years in 1990, and 9,438 and 40,116 respectively in 2022. For clarity, the age-related fertility rates (live births per 1000 women) are presented in Table 2.

It is obvious that teenage pregnancy rates have decreased, but they still remain a serious problem in the Russian Federation. There is also a decreased rate of abortions. Thus, it was 0.3 per 1,000 up to 15 years old and 8 per 1,000 for 15–17 years old in 2015 and 0.2 and 3.5 in 2022, respectively [8]. This is due to the contraceptive revolution, availability of information, sexual education and a more trusting relationship with parents.

According to The Bulletin of the World Health Organization devoted to teenage pregnancy, risk factors for pregnancy in minors can be divided into two groups: social and economic. Social factors include poor living conditions and quality of life, low level of education, early marriages, violence, a weak level of security, and difficulties in family relations. Economic factors include the lack of financial opportunities to purchase contraceptives, obtain accessible information and medical examination.

Teenagers can take the news of pregnancy hard, and their behavior in such situations is unpredictable. It is extremely important to establish emotional understanding and determine whether a teenager is prone to suicidal thoughts.

In a study by Coleman and co-authors, which covered 877,181 women, including 163,831 women who underwent abortions, it was found out that 81% of women who survived an abortion had an increased risk of mental disorders [9].

In total, 503.8 thousand cases of abortions were registered in Russia in 2022. Though the figure was high, these data are one third lower compared to 836.6 thousand cases in 2015 [8]. Of these, 200 and 3,500 cases were performed among girls under 15 years old and in the age group from 15 to 17 years old in 2022, respectively. Adolescents face a higher risk

Table 1. The number of live births by the maternal age and the order of birth in the Russian Federation in 2022

Maternal age (years)	Total live births	Including the order of the child's birth:			
		The first	The second	The third	The fourth
12	3	3			
13	26	25	1		
14	207	204	3		
15	775	748	27		
16	2327	2206	115	5	
17	6336	5796	489	31	5
18	14584	12975	1389	146	11
19	25532	21786	3300	339	36

Source: Rostat, 2022

Table 2. Age-related fertility rates

Year	Live births per 1,000 women, years of age	
	15–17	18–19
1990	17.8	112.8
2,000	10.0	55.3
2010	10.4	46.3
2015	9.1	45.3
2022	4.3	27.3

Source: Demographic Yearbook of Russia, 2023

of abortion-related complications. This applies to both physical and emotional risks, with possible immediate, short-term and long-term consequences. Long-term consequences for the mother include an increased risk of death, suicide attempts, cancer, coronary heart disease, violent actions, alcohol, drug and psychoactive substance abuse. In children born to teenage mothers, a high risk is associated with impaired health and cognitive functions, low academic achievement, likelihood of teenage pregnancy in girls and a tendency to commit crimes in boys.

Teenagers are 6 times more likely to attempt suicide if they have had an abortion in the last six months, as opposed to those who have not done so, and are four times more likely to commit suicide than adults who terminate a pregnancy [10, 11].

It is important to carry out regular screening of emotional disorders (Edinburgh Postnatal Depression Scale, Beck Inventory and others) and psychological counseling within 6–12 months after childbirth or termination of pregnancy [12].

Paradoxically, in dysfunctional families, there are rare conflicts with health care institutions over the lack of information about the health status of a minor [13]. Parents who are detached from the parenting process or single parents often do not show any interest in premature initiation of sexual life by their children and potential dangers associated with it. In families that seem to be prosperous at first glance, conflicts with medical institutions are more frequent, especially in cases where a teenager tries to solve own problems without involving parents. This is typical for families where parenting is based on strict rules and restrictions. Interestingly, those who choose abortion usually have a higher socioeconomic status, strive for educational and professional development, higher self-esteem, more control over their lives, experience less anxiety and are better able to plan their future compared to teenagers who decide to become parents [14].

According to article 54 on the rights of the minors in the field of health protection of Federal Law No. 323-FZ [15], 'minors over the age of fifteen or drug-addicted minors over the age of sixteen are entitled to provide informed voluntary consent to medical intervention or refuse to do so'. Thus, a teenage girl over the age of 15 has the right to be registered for prolongation or termination of pregnancy. As for medical secrecy, until 2020, it was indeed unacceptable to disclose information about pregnancy to the legal representatives of the girl (parents, adoptive parents, guardians or guardians) over the age of 15. But, according to the amendments to Article 22 of the Federal Law 'On the Basics of protecting the health of Citizens in the Russian Federation', 'in respect of persons who have reached the age established by part 2 of Article 54 of this Federal Law, but have not acquired full legal capacity, information on the state of health is provided to these persons and to their legal representatives, if these persons haven't reached the age of majority'.

That is, if the girl does not want to inform her legal representatives about the pregnancy, then the legal representative can still receive this information upon request.

According to the list of medical indications for artificial termination of pregnancy, [16] termination is limited to 22 weeks. If the period of pregnancy exceeds 22 weeks, the issue of termination of pregnancy is decided individually by a council of doctors. But what should be done if opinions about the preservation of pregnancy in a girl under 15 years of age and legal representatives do not coincide? Let's consider two situations: the first, when the girl wants to terminate the pregnancy, and the parents want to keep it, and the second, when the girl wants to keep the pregnancy, and the parents do not want to agree with this decision. In the first case, the minor pregnant woman under the age of 15 will have to keep pregnancy even against her will, but in the second case she has the right to keep it without the consent of legal representatives according to Article 22 of the Constitution of the Russian Federation [17] on the physical immunity of the person, when 'anyone has the right to make independent decisions about actions regarding their body'. That is, compulsory intervention can occur only in cases where it is necessary to save the life of the pregnant woman herself.

In contrast, minors between the ages of 15 and 18 can independently make decisions about termination of pregnancy or other medical procedures without the need to obtain consent from legal representatives. This discrepancy in the requirements for girls under 15 years of age and older results in a problem: on the one hand, it is necessary to maintain confidentiality, medical secrecy about a minor, and on the other hand, parents must be informed as they are able to influence their children's decisions [13].

The peculiarities of managing teenage pregnancy also include late presentation for antenatal care: 22.4±7.5 weeks for 13–15 years and 15.8± 6.9 weeks for 16–17 years [18]. It is a matter of concern that, although 91% of adolescent girls aged 15–17 years have received formal sex education on contraception and abstinence, 83% reported that they did not receive this kind of education before the first sexual intercourse [3].

CONCLUSION

A review of the literature has identified key factors contributing to teenage pregnancy, such as low social and economic status, lack of sexual education and limited access to contraceptives. An analysis of statistical data has shown a decrease in the rate of teenage pregnancy during the recent years, which is associated with improved access to contraceptives and increased contraceptive awareness among adolescents.

Despite the positive trends, the problem of teenage pregnancy remains relevant. Many adolescents continue facing social and economic barriers that prevent access to health services and information. In addition, insufficient attention is paid to the psychological support of young mothers and their children, which can negatively affect their long-term health and well-being.

The task of preserving the reproductive health of children and adolescents continues to be one of the most significant problems in modern society.

Pregnant adolescents need special attention and require additional care at all stages of pregnancy management or termination, childbirth and postpartum period. It is essential to have conversations about the safety and effectiveness of contraception in the postpartum period to prevent repeated unwanted pregnancies shortly after delivery. In order to achieve these important goals, collaborative efforts of the medical community, educational institutions, parents and society are required. Raising awareness about reproductive health, availability of high-quality contraceptive advice and comprehensive support for pregnant adolescents and young mothers should become priorities in public policy and health. This is the only way to achieve significant progress in preserving and strengthening the reproductive health of the younger generation.

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THE ETHICAL ASPECT OF WORKING WITH AUDIOLOGY PATIENTS: THE RELATIONSHIP BETWEEN HEARING AND COGNITIVE FUNCTION

Vinogradova MV ✉

Pirogov Russian National Research Medical University, Moscow

Currently, the prevalence of hearing loss in the population is extremely high both among elderly and younger patients due to the prolonged and intense load on the auditory analyzer. Auditory disorders are currently one of the most important geriatric and ethical problems, since it has a significant negative impact on a human's emotional and physical condition, and is the cause of conflicts with other people. According to the research done in recent decades, there is a relationship between hearing loss and cognitive decline, which can be assessed using the MCAS (Montreal Cognitive Assessment Scale) test. This article presents a clinical case of a patient with progressive sensorineural hearing loss and, as a result, a decrease in cognitive functions, as well as the ethical aspect of the work of an ENT specialist with audiology patients.

Key words: hearing loss, cognitive function, ethical issue, sensorineural hearing loss

✉ **Correspondence should be addressed:** Maria V. Vinogradova
Ostrovityanova str., 1, Moscow, 117997, Russia; drmvinogradova@gmail.com

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ЭТИЧЕСКИЙ АСПЕКТ В РАБОТЕ С СУРДОЛОГИЧЕСКИМИ ПАЦИЕНТАМИ: СВЯЗЬ МЕЖДУ СЛУХОМ И КОГНИТИВНОЙ ФУНКЦИЕЙ

М. В. Виноградова ✉

Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва

В настоящее время распространенность потери слуха населения крайне высока — как у пациентов преклонного возраста, так и у более молодого контингента в связи с длительной и интенсивной нагрузкой на слуховой анализатор. Слуховые нарушения являются на сегодняшний день одной из важных гериатрических и этических проблем, поскольку она оказывает значительное негативное влияние на эмоциональное, физическое состояние человека, является причиной конфликтов с окружающими людьми. Согласно исследованиям последних десятилетий, есть взаимосвязь между потерей слуха и снижением когнитивных функций, оценить которую можно благодаря МоСА-тесту (Монреальская шкала когнитивной оценки). В данной статье приведен клинический случай пациентки с прогрессирующей нейросенсорной тугоухостью и, как следствие, со снижением когнитивных функций, а также этический аспект работы врача-оториноларинголога с пациентами сурдологического профиля.

Ключевые слова: нейросенсорная тугоухость, когнитивне функции, этическая проблема, снижение слуха

✉ **Для корреспонденции:** Мария Вячеславовна Виноградова
ул. Островитянова, д. 1, г. Москва, 117997, Россия; drmvinogradova@gmail.com

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Currently, the prevalence of hearing loss among the elderly is very high: up to 30% of men and 20% of women by the age of 70 and 55% of men and 45% of women over the age of 80 have hearing loss of at least 30 decibels (dB). But taking into account the scientific and technological progress, the use of headphones, including in-ear headphones, and long-term listening to loud music, the number of cases of hearing loss in younger people is growing [1].The average number of unilateral deafness is varied from 12 to 20 cases per 100,000 population (3–6%) [2].This hearing loss first affects high frequencies [3] which, in a mild form, leads to problems during conversations in noisy environments, and as it worsens, difficulties arise in any conversation due to problems with word differentiation and even voice identification [3, 4]. With time, it has been observed that hearing loss is associated with depressive symptoms, impaired communication and social relationships, as well as with increased difficulties in everyday life [5]. Sensory impairments, including hearing loss, are considered one of the main geriatric problems, since the loss has a significant negative impact on a person's emotional and physical condition [6–8], and is the cause of conflicts with other people. In this regard, patients rarely go to the doctor right away, blaming age for the problems that have appeared. The same applies to dementia conditions and milder forms of decreased intelligence in the form of decreased cognitive functions developed for a long time, and the patient does not notice them, and in later stages he does not have the opportunity to critically assess his condition, and therefore gets to a doctor's appointment in such a state when the recovery reserve is already extremely small. Some other geriatric diseases, such as osteoporosis and cataracts, have a vivid clinical picture. Thus, the patients often consult a doctor more frequently, which allows to correct the conditions at early and uncomplicated stages. This article presents a clinical case of a patient with progressive sensorineural hearing loss and, as a result, a decrease in cognitive functions, as well as the ethical aspect of the ENT specialist's work with audiology patients.

In studies of the last 5 years [9], there has been a pronounced impairment of cognitive functions (CF) at an accelerated pace as compared to people with normal hearing. For the first time, the connection between the auditory function and cognitive abilities was mentioned in 1964 by a group of scientists headed by Kay D [10], and then, for almost 20 years, this topic was never reviewed. In 1989, a group of authors published a study that proved there is a link between hearing loss and progressive cognitive decline, whereas the socially significant amount of hearing loss was more than 40 dB [11]. Later, more fundamental works were published that suggested a link between hearing loss and deterioration of

cognitive functions due to physiological aging of the brain, which was confirmed by the presence of certain changes in magnetic resonance imaging of the brain [12]. Despite the impressive number of conducted studies, a major review of which was conducted in 2016 by Roberts, et al [13], the pathogenesis and relationship between hearing loss and progressive decrease in CF are not fully clear. Previously, it was believed for a long time that patients suffering from unilateral hearing impairment or loss required no rehabilitation measures, however, based on the results of the above studies, a logical question was posed: 'Will the level of CF change if the hearing level is stopped or restored?' At the moment, the only rehabilitation tools for deaf patients include a hearing aid and cochlear implantation (CI). Unfortunately, at the moment the indications for CI are strict, therefore, candidates for CI can only be people with severe hearing loss, such as bilateral deep sensorineural deafness (the average threshold of auditory perception at speech frequencies is more than 95 dB), the lack of a pronounced effect from properly selected hearing aids (binaurally), the absence of severe somatic diseases, cognitive and mental problems, as well as readiness for long-term rehabilitation after CI supported by relatives. The effect of rehabilitation measures can be seen in the study [14], which involved 94 patients who underwent CI, and then assessed CF and other life quality indicators: it was found out that intervention in the form of CI among the elderly led to an improvement in preoperatively impaired CF at months 6 and 12 after CI. In 2019, a large study was conducted at the St. Petersburg Research Institute of the Department of ENT Diseases [9] to assess mental health and quality of life in adult patients with acquired unilateral deafness using PHQ-9 (allow to identify the level of depression in a patient, consists of 9 questions and evaluates the mental state in a two-week period, as well as the need for prescribing drug therapy) and GAD-7 questionnaires (make it possible to determine the level of anxiety in the interviewee. The questionnaire consists of 7 questions. The patient must determine the frequency of presented conditions two weeks prior to the test), and PSQ (allows you to assess the stress level of the respondent. The patient must answer 30 questions presented in the questionnaire, without thinking or predicting the likelihood of a situation in the future), HHIA (widely used to assess the quality of life in adult patients with hearing impairment). According to the results of the study, it was revealed that patients with acquired unilateral deafness have increased levels of stress and anxiety, and suffer from depression. Patients with unilateral deafness are not satisfied with the quality of life in general, and hearing problems mostly affect the emotional and social aspects of life. There are also various questionnaires and scales for assessing CF, but the Montreal Cognitive Assessment Scale (MCAS) is most often used in clinical practice. This scale is designed for the rapid diagnostics of mild cognitive impairment. It evaluates various cognitive functions, namely attention and concentration, executive functions, memory, speech, optical and spatial activity, conceptual thinking, counting and orientation. This test takes about 10 minutes, which allows you to use this method of examination in the routine admission of patients. For people who have pronounced (3–4 degrees) bilateral hearing loss, an adapted HI-MCAS test has been developed where all voice commands have been replaced by text commands that are displayed on the screen of the subject.

DESCRIPTION OF THE CLINICAL CASE

A 63-year-old woman came to the clinic for an outpatient appointment with an ENT specialist complaining of hearing impairment and increased high-frequency noise in her right ear, which prevented from falling asleep and reduced concentration, as well as periodic attacks of dizziness and periodic headaches. This exacerbation has been a problem for about 3 months. It is known from the anamnesis that the patient has been observed by an otorhinolaryngologist for 2 years with a diagnosis of 2nd degree chronic sensorineural hearing loss on the right and vestibulopathy of unknown origin. According to the clinical recommendations on sensorineural hearing loss [15], the patient underwent a complex examination. It included as follows: otoscopy (no pathology detected), an audiological examination — 2 degree right-sided sensorineural hearing loss (average hearing threshold of 45dB), bilateral type A tympanometry, ipsilateral reflexes were preserved bilaterally, magnetic resonance imaging of the brain (no data for the formation of the bridge-cerebellar angle were revealed, single vascular foci of white matter were found). The patient was consulted by a neurologist, who conducted a MCAS with 27 score level (moderate cognitive impairment) and diagnosed with 1-degree dyscirculatory encephalopathy of mixed genesis, migraine without aura. The patient was prescribed anxiolytic drugs (Grandaxin), which the patient did not take, as well as vascular and metabolic therapy (Mexidol, Cerebrolysin); lifestyle recommendations were given. The last audiological control was more than a year and a half ago. It is worth noting that according to the clinical recommendations on sensorineural hearing loss, patients with this diagnosis are recommended to undergo an audiological examination at least once a year in order to control their auditory function and timely correct the auditory deficit. During the visit, a repeated audiological examination was performed with 3–4 degree right-sided sensorineural hearing loss and pronounced hearing loss at speech frequencies of up to 63 dB (from 500 Hz to 4,000 Hz). According to the repeated MCAS test, 22 points were assigned (mild dementia). Based on complaints of periodic dizziness and headache, as well as the diagnosis of migraine without aura established by a neurologist, additional examinations of the vestibular apparatus were conducted such as videonystagmography and caloric tests. No pathology was identified, but anamnestic data in the form of periodic dizziness and headache indicate at a probable vestibular migraine. When discussing the results of the examination, prognosis of the disease, and recommendations, and namely, while establishing an auditory prosthesis on the right to improve speech intelligibility and suppress the noise, the patient showed aggression towards the doctor and expressed distrust in the established diagnosis. In such cases, the doctor needs to explain the benefits of recommendations and prescriptions to the patient in detail. In case of repeated aggression and disagreement of the patient, it makes sense to consider the patient's referral to a psychiatrist / psychotherapist as an otorhinolaryngologist's consultation is time-limited.

DESCRIPTION OF THE CLINICAL CASE

According to the study [16], such an aggressive reaction to diagnosis and a decrease in CF is included in the clinical picture at the initial stage of behavioral frontotemporal dementia. In such an extremely sensitive situation, the doctor must tactfully refer this kind of patient to a dedicated expert, but, as a rule, in most patients, referral to a psychiatrist is stigmatized as they are sent to a psychiatric hospital, lose respect and trust of others, and are prescribed potent drugs. At this stage, the doctor needs to find out the patient's fears, select arguments and counterarguments that will help the patients change their position, calm down, and win over. To do this, the doctor

must be familiar with the law of the Russian Federation 'On Psychiatric Care and Guarantees of citizens' rights in its provision' No. 3185-1 dated 07/02/1992, which provides clear explanations on how psychiatric care is currently provided.

In this clinical case, the patient was convinced of the expediency of prescriptions and recommendations. The patient referred to an ENT specialist 6 months after a hearing aid selection and use, and conduction of therapy. The MCAS test was performed during the visit with 25 points being scored (moderate cognitive impairment), which shows an improved cognitive function and patient compliance.

CONCLUSIONS

Thus, the above clinical case showed the existing relationship between impaired hearing loss and progressive decrease in CF, and the MCAS test turned out to be the optimal diagnostic tool for routine admission, and the importance of an individual approach to each deaf patient, supported by knowledge of legislation, is demonstrated. The information obtained can help otorhinolaryngologists, surdologists, and general practitioners provide timely and ethically correct care to patients with hearing impairment.

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BIOMEDICAL RESEARCH INVOLVING ELDERLY SUBJECTS: ETHICAL ASPECTS

Semenova NV ✉

Bekhterev National Research Medical Centre for Psychiatry and Neurology, St. Petersburg, Russia

Due to the aging of the population and growing proportion of the elderly, medicine requires a more active and purposeful approach not only to study theoretical aspects of gerontology, but also to search for new drugs designed specifically for this category of the population. Clinical trials in older people are more in demand than ever. However, researchers must ensure that they conduct their studies ethically. Key ethical issues include prevention of discrimination and violations of the autonomy of older people, as well as special requirements for informing and obtaining voluntary informed consent. When preparing voluntary informed consent for older people, especially for those with cognitive decline, special attention should be paid not only to the information itself, but also to the form of its presentation. The documents should be concise, clear and contain all the key information. In addition, the use of modern multimedia technologies can help the subjects make an informed decision about their participation in the study. For patients with cognitive impairment, it is important to adhere to the principle that the higher the risk for the study participants, the more the patient's cognitive functions and decision-making ability should be preserved. Excluding patients from studies with potential benefit due to age or cognitive impairment is considered unethical and discriminatory. This is taken as an unfair restriction of their access to the achievements of scientific and technological progress in the field of medicine.

Keywords: ethics, old age, vulnerable patients, cognitive impairment, informed consent

✉ **Correspondence should be addressed:** Natalia V Semenova
Bekhtereva Str., 3/1, St. Petersburg, 192019, Russia; nvs@bekhterev.ru

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БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ С УЧАСТИЕМ ПОЖИЛЫХ ЛЮДЕЙ: ЭТИЧЕСКИЕ АСПЕКТЫ

Н. В. Семенова ✉

Национальный медицинский исследовательский центр психиатрии и неврологии им. В. М. Бехтерева, Санкт-Петербург, Россия

Старение населения и увеличение доли пожилых людей среди населения ставят перед медициной необходимость в более активном и целенаправленном подходе не только к изучению теоретических аспектов геронтологии, но и к поиску новых лекарств, предназначенных специально для этой категории населения. Все более востребованными становятся клинические исследования с участием пожилых людей. Однако проведение таких исследований требует особого внимания к этическим аспектам. Ключевые этические вопросы включают предотвращение дискриминации и нарушений автономии пожилых людей, а также особые требования к информированию и получению добровольного информированного согласия. При подготовке добровольного информированного согласия для пожилых людей, особенно с проявлениями когнитивного снижения, особое внимание следует уделять не только самой информации, но и форме ее представления. Документы должны быть краткими, понятными и содержать всю ключевую информацию. Кроме того, использование современных мультимедийных технологий может помочь испытуемому принять обоснованное решение относительно своего участия в исследовании. Для пациентов с когнитивными нарушениями важно придерживаться принципа, согласно которому чем выше риск для участников исследования, тем в большей степени должны быть сохранены когнитивные функции пациента и способность принимать решения. Исключение пациентов по причине возраста или «когнитивной недостаточности» из исследований, в которых они потенциально могли бы извлечь пользу, считается неэтичным и дискриминационным. Это рассматривается как несправедливое ограничение их доступа к достижениям научно-технического прогресса в области медицины.

Ключевые слова: этика, пожилой возраст, уязвимые пациенты, когнитивные нарушения, информированное согласие

✉ **Для корреспонденции:** Наталия Владимировна Семенова
ул. Бехтерева, д. 3/1, г. Санкт-Петербург, 192019, Россия; nvs@bekhterev.ru

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The progressive increase in the proportion of older age groups is an important demographic trend that causes a natural increase in the proportion of specific diseases of late age, especially cognitive disorders. According to Rosstat, the number of people over 65 in the Russian Federation was 16% as of 01.01.2022 (taking into account the results of the All-Russian Population Census in 2020). In the future, the proportion of elderly people in Russia, and especially of those aged 80 and older, will be increasing [1]. As the Russian population ages, the importance of research devoted to the aging process, conditions and diseases that are especially common in older people, is becoming increasingly important. The Ethics Committee (CE) faces a number of questions regarding participation of older people in research. The most important one is as follows: "*Do older people need special protection, and if so, when?*". The CE must maintain a balance between the necessary need for protection and respect for these people [2].

In addition to the requirements for providing special protection to vulnerable segments of society [3], which are guided by the CE, there are no special standards or Russian laws for conducting research on the elderly. According to the general opinion, the elderly represent a heterogeneous population, which, as a rule, does not require any special protection, except for two cases:

- people with cognitive impairments;
- persons located in specialized medical institutions.

In these cases, the approach to these study participants will be the same as to others under the same circumstances.

There is no specific age starting from which elderly patients are considered unsuitable for research. Some of them may not have clinically pronounced cognitive impairments and related disorders of daily functioning. However, some researchers try to avoid involving the elderly in research due to certain difficulties in their selection. Older people tend to avoid participating in the research that disrupts their normal daily routine, is inconvenient or does not directly benefit them. Also, conducting a study involving elderly patients may be more difficult and expensive.

Older people may have problems with vision, hearing and speech. Thus, it may take more time to explain to them the tasks of participating in the study. They interrupt their participation in research more often than young people, so it is necessary to initially screen more participants.

Despite these difficulties, it is necessary to include older people in research. If they are excluded or treated with special methods, the doctor must make sure that they are protected and not treated in a contemptuous, stereotypical or patronizing manner. The tasks of the CE are to conduct an ethical examination and recommend conducting a study for this category of patients, taking into account all possible risks both for the studied drug and for the procedures.

Screening and diagnostic procedures, as well as therapies, are becoming more complex and diverse. So, the question of adequate and accessible information for patients about the methods used, adverse events and all other diverse aspects included in the procedures of clinical research is becoming more acute. Thus, obtaining the informed consent of an elderly patient, especially if there are problems with cognitive functioning, becomes not just a discrete procedure carried out before the start of any research procedures, not just a legal and ethical requirement, but an ongoing process based on the relationship between the researcher and the patient. Owing to the informed consent, the patient obtains an optimal opportunity to take an autonomous decision that best suits his beliefs and preferences.

The CE should treat the cognitive impairments of older people in the same way as it treats any other potential research participants. Elderly people with cognitive impairments can be involved in research only under the following circumstances:

- when other groups of people are not suitable for research;
- if the study is related to the problem seen only among patients with similar disorders;
- if the study entails a minimal risk only.

Using age as a criterion for the ability to give consent and thus participate in the study is unjustified. And although it is recognized that memory impairment can be a problem for some older people (thus, their ability to constantly express their willingness to participate in the study is being questioned), the task of the CE is to determine *if older people can make informed choices*

Numerous experimental and psychological studies are consistent with household observations that elderly people are worse at learning new information compared to young people. In older patients, memory impairment is combined with a number of other changes in cognitive functions. The latter relate primarily to reaction time, which tends to increase with age. As a result, older people need more time to do a similar amount of mental work as compared to younger people. In older age, fatigue during mental exercises also develops somewhat faster than in younger people. The main causes of cognitive impairment in older age are various neurodegenerative (primarily Alzheimer's disease), cerebrovascular diseases and dysmetabolic disorders [4, 5]. The prevalence of moderate cognitive impairment among people aged 60 years and older ranges from 5.0 to 36.7% [6].

There are four types of impaired decision-making ability that are taken into account when planning and conducting scientific research in patients with cognitive disorders:

1) the fluctuating is seen in some conditions, when painful symptoms periodically increase and decrease;
2) the prospective is found at the early stages of Alzheimer's disease, when the symptoms are steadily increasing and, despite the existing ability to make decisions at this time, there are compelling reasons to expect violations in the future;
3) the limited relates to more advanced stages of Alzheimer's disease, when the ability to express informed consent is impaired, but the subject is still able to express "less qualitative" consent (assent) or refuse to participate in the study;
4) the complete is about the final stages of Alzheimer's disease, deep dementia, when almost any ability to make decisions based on any significant reflection is lost [7, 8].

For patients with cognitive impairment, it is important to adhere to the principle that the higher the risk for the study participants, the more the patient's cognitive functions and decision-making ability should be preserved. In other words, patients with more pronounced cognitive disorders may be included in studies where the risk is no more than minimal. Patients with cognitive impairment, even if they are legally capable, should not be involved in the same studies where the possible risk is high and where confidence is required that, by agreeing to participate in the study, an elderly patient understands all the features of the study associated with a possible risk.

Though in the second half of the 20th century bioethics focused on the balance of risk and benefit in research, in the beginning of the 21st century, increasing attention is being paid to ethical aspects such as providing access to new, advanced medical technologies and medicines to vulnerable patients in particular need. Therefore, excluding patients from studies where they may receive potential health benefits due to a certain age or cognitive insufficiency seems unethical. Today, their exclusion from research is considered as discrimination and unfair restriction of their access to scientific and technological progress in the field of medicine [2, 3].

When preparing informed consent for older people, especially those with cognitive decline, the following fundamental points should be taken into account. Special attention should be paid not only to the information contained in the consent form, but also to how this information is submitted. Researchers should create concise and understandable documents with the key information that causes no different interpretations of its content. This can help the subject to make the right decision about the possible participation in the study [9]. Often, improvements of informed consent forms are associated with the use of modern multimedia technologies (for example, slide shows, short video presentations, questionnaires, audio recordings of the key information, etc.). It helps to present the content of the document in a more concise and visual manner and to improve the understanding of specific medical information by potential research participants.

In cases where an elderly patient cannot read the text of the informed consent form himself, the researcher must read this information in full and answer all questions that arise. During the procedure of informing and obtaining informed consent, the presence of an impartial witness is required. The witness must not be the researcher's subordinate or relative. The witness confirms that the informed consent form was fully read to the patient and understood by him in the witness presence, and that the patient had the opportunity to ask any questions and get answers. The impartial witness, along with the patient and the researcher, must also sign and date the informed consent form.

Some of the features associated with obtaining consent from older people include methods of providing information, written or oral. A quite high level of reading skills is required to understand the informed consent form. As far as discussion of the consent form goes, a clear and understandable explanation should contain simple terms, lack of professional and other jargon, and willingness to answer any questions, regardless of whether the patient has a cognitive impairment or not.

If necessary, it is recommended to use additional methods to help the subject better understand information about

the nature of scientific research and the consequences of their participation herein. They include repeated provision of information, use of educational videos, group discussion with patients who previously participated in similar studies, etc.

Structured procedures prevail among the methods that contribute to a better understanding of the consent form. They are as follows: specially designated question-and-answer sections, interactive presentations with the possibility of preview, and questionnaires regarding the consent form. Often, improvements in the field of informed consent forms are associated with the use of modern multimedia technologies (for example, slide shows, short video presentations, questionnaires, audio recordings of the consent process, etc.), which helps to present the content of the document in a more concise and visual manner and to improve the understanding of specific medical information by potential research participants.

As soon as the question of decision — making ability arises, the clinician's task is to determine this ability as accurately as possible. It should be taken into account that a universal tool for evaluating this function has not yet been created. Therefore, if there are certain doubts, a consultation with colleagues may be a good idea.

Elderly patients, including those with cognitive impairments, can participate in the "caregiver" study. The caregiver (accompanying person) may be a family member or other relative, neighbor, friend, or close person who will help the patient cope with the research procedures, come to the research center for visits and provide the researcher with the necessary information about changes in the patient's condition. Before being included into the study, the caregiver must sign and put a date on a special, separate informed consent form for the caregiver, which provides information about the essence of the study, its procedures, as well as describes the responsibilities of the caregiver and, if necessary, compensation for his expenses (for transport, food, etc.). Just like the main participant in the study, the caregiver can withdraw from further participation in the study at any time. In such a situation, however, there may be a risk that the patient will not be able to continue participating in the study without an accompanying person. Therefore, when considering candidates for caregivers, the researcher needs to make sure that the person will be able to perform quite long-term duties of accompanying the patient in the study based on the physical and psychological condition. At the same time, it must be clearly understood that the caregiver cannot be the legal representative of the patient and make any decisions regarding participation or non-participation in the study and its procedures for the patient.

Both clinicians and researchers should be aware of the ethical issues associated with decision-making by elderly patients. It is necessary to take into account the possible violations of cognitive functions responsible for the quality of decision-making. When elderly patients are included in the study, it is important to make sure that their decision-making is autonomous, has no outside influence and coercion, which in its turn can increase the confidence of this group in biomedical research. The possibility of further progress in the treatment of elderly diseases largely depends on the willingness of this cohort to participate in clinical trials.

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A REPRODUCED COMBINATION OF IVACAFTOR AND LUMACAFTOR, CFTR PROTEIN MODULATORS. ETHICAL AND PHARMACOKINETIC ASPECTS

Noskov SM[1], Radaeva KS[2] ✉, Arefeva AN[2]

[1] Clinical Hospital No. 3, Yaroslavl, Russia

[2] Pharm Holding CJSC, St. Petersburg (Pharm Holding CJSC), Russia

The lack of effective and affordable therapies for rare diseases is an important ethical issue. One example is cystic fibrosis (CF), a chronic, progressive disease characterized by an impaired function of all exocrine glands. The combination of ivacaftor and lumacaftor (CFTR potentiator and corrector) should lead to a sufficient level of protein on the cell surface and to an increase in its activity, thereby correcting the impaired function. Development of a generic drug containing ivacaftor and lumacaftor as active pharmaceutical substances will increase the availability of this medication and improve patient survival. To study comparative pharmacokinetics and bioequivalence of drugs containing ivacaftor and lumacaftor in healthy volunteers. It was conducted as an open-label, randomized, crossover bioequivalence study involving a single intake of the drug during each period under fed condition in healthy male and female volunteers. The conclusion about bioequivalence was made if 90% confidence interval for primary pharmacokinetic parameters (C_{max}, AUC_{0-t}) fell within the accepted bioequivalence limits of 80–125%. According to the results of the study, it was shown that the values of 90% CI of the geometric mean of the main pharmacokinetic parameters for ivacaftor and lumacaftor fall within the acceptance limits for bioequivalence. According to the applied criteria, the drugs are bioequivalent, which makes it possible to recommend the investigational drug to the Ministry of Health of the Russian Federation for obtaining the registration status.

Key words: bioequivalence, cystic fibrosis, CFTR, pharmacokinetics, ethics

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Compliance with ethical standards: the condition for conducting the clinical trial was authorization from the Ministry of Health of the Russian Federation No. 212 dated 04/17/2023 and approval of the study by Independent Ethics Committee (excert from the meeting protocol of the Ethics Committee No. 325 dated 01/17/2023). All the essential trial documents (protocol GP30511-P4–01–01, Investigator’s Brochure, written information given to trial subjects and informed consent form, volunteer life and health insurance certificate) were provided and approved by the Independent Ethics Committee (IEC) of the research center according to the procedures of this committee. The researchers are obliged not to disclose personal and medical data of the subjects. Prior to the start of any trial procedures, an informed consent procedure was carried out in accordance with the principles of the Declaration of Helsinki, ICH recommendations and national regulatory standards. Each volunteer included in the study was insured and must have received an original insurance certificate.

✉ **Correspondence should be addressed:** Kseniia S Radaeva
Svyasi Str., 34a, Strelna village, Saint-Petersburg, 198515, Russia; Kseniia.Radaeva@geropharm.com

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ВОСПРОИЗВЕДЕННАЯ КОМБИНАЦИЯ МОДУЛЯТОРОВ БЕЛКА CFTR — ИВАКАФТОРА И ЛУМАКАФТОРА. ЭТИЧЕСКИЕ И ФАРМАКОКИНЕТИЧЕСКИЕ АСПЕКТЫ

С. М. Носков[1], К. С. Радаева[2] ✉, А. Н. Арефьева[2]

[1] Клиническая больница № 3, Ярославль, Россия

[2] ЗАО «Фарм-Холдинг», Санкт-Петербург, Россия

Отсутствие эффективной и доступной терапии для редких заболеваний является важной этической проблемой. Одним из примеров является муковисцидоз (МВ) — хроническое, прогрессирующее заболевание, характеризующееся нарушением функции всех экзокринных желез. Комбинация ивакафтора и лумакафтора (потенциатора и корректора CFTR) должна приводить к достаточному уровню белка на поверхности клетки и к увеличению его активности, тем самым корректируя нарушенную функцию. Разработка воспроизведенного препарата, содержащего в качестве активных фармацевтических субстанций ивакафтор и лумакафтор, позволит увеличить доступность данного препарата и улучшить выживаемость пациентов. Изучение сравнительной фармакокинетики и биоэквивалентности препаратов, содержащих ивакафтор и лумакафтор у здоровых добровольцев. Данное исследование проводилось как открытое, рандомизированное, перекрестное исследование биоэквивалентности с однократным приемом препарата после еды у здоровых добровольцев обоих полов. Вывод о биоэквивалентности был сделан, если при оценке 90% доверительных интервалов для первичных фармакокинетических параметров (C_{max}, AUC_{0-t}) они находились в принятых границах биоэквивалентности 80–125%. По результатам исследования было показано, что значения 90% ДИ для отношений геометрических средних основных фармакокинетических параметров для ивакафтора и лумакафтора укладываются в допустимые пределы биоэквивалентности. Согласно применяемым критериям, препараты являются биоэквивалентными, что позволяет рекомендовать тестируемый препарат в МЗ РФ для получения регистрационного статуса.

Ключевые слова: биоэквивалентность, муковисцидоз, CFTR, фармакокинетика, этика

Финансирование: исследование финансировалось ООО «ГЕРОФАРМ».

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Соблюдение этических стандартов: условием для проведения клинического исследования являлись Разрешение МЗ РФ № 212 от 17.04.2023 и одобрение исследования Советом по этике (выписка из протокола заседания Совета по этике № 325 от 17.01.2023). Все основные документы исследования (протокол GP30511-P4-01-01, брошюра исследователя, информационный листок здорового добровольца и форма информированного согласия, документы по страхованию жизни и здоровья добровольцев) были предоставлены и одобрены Независимым этическим комитетом (НЭК) исследовательского центра, согласно процедурам этого комитета. Исследователи взяли на себя обязанность неразглашения личных и медицинских данных субъектов. До начала любых процедур исследования была проведена процедура получения информированного согласия, которая соответствовала принципам Хельсинской декларации, правилам ICH и национальным регуляторным стандартам. Каждый доброволец, включенный в исследование, был застрахован и обязательно получил оригинал полиса страхования.

✉ **Для корреспонденции:** Ксения Сергеевна Радаева
ул. Связи, д. 34а, пос. Стрельна, г. Санкт-Петербург, 198515, Россия; Kseniia.Radaeva@geropharm.com

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One of the important ethical dilemmas is the lack of effective and safe therapy for orphan diseases [1]. Although rare diseases occur individually with a low frequency, they collectively affect a significant part of the population. Due to the low prevalence, patients with orphan diseases experience many difficulties related to both the severity of the disease and the lack or low availability of appropriate treatment. When combined, these factors infringe on the right of such patients to receive qualitative medical care and thereby exacerbate inequality and vulnerability of affected patients, which is unacceptable from the perspective of medical ethics. Cystic fibrosis (CF) is an example of such a disease. CF is a chronic, progressive autosomal recessive disorder associated with impaired transport and secretion of chlorine ions, which leads to a change in the electrolyte composition and dehydration of the secretion of the endocrine glands. CF is characterized by damage to all exocrine glands and other vital organs and systems. Currently, one in 9,000 newborns in the Russian Federation (RF) is diagnosed with CF and, according to the registry, there are about 4,000 patients with this pathology in the RF [2].

The disease is developed due to mutations in the gene of the *Cystic Fibrosis Transmembrane Conduction Regulator (CFTR)* protein. More than 2,000 types of mutations have been currently identified. The most prevalent mutation in the RF is a deletion within the reading frame, leading to the loss of phenylalanine at position 508 in the *CFTR* — F508del *protein*. This mutation occurs in 52.79% of cases and, according to some data, at least one copy of it has been registered in about 90% of patients with cystic fibrosis [3]. This mutation belongs to type II mutations and results in abnormalities in protein processing, localization and transport to the apical membrane of cells [3, 4].

Conventional approaches of CF therapy are mainly focused on addressing the underlying symptoms. Pancreatic insufficiency is well compensated by enzyme substitution therapy and adherence to a specialized high-calorie diet [5]. The bronchopulmonary process is treated with antibacterial, including inhaled kinesitherapy methods, used to improve the drainage of secretions in the distal parts of respiratory tract, mucolytic drugs, inhaled bronchodilators, and in some cases — hormonal therapy with glucocorticosteroids are also used. The discovery of molecules that modulate the CFTR activity marked a new era in the treatment of CF, since this is the first option to therapeutically target a defective CFTR protein, rather than treating complications caused by the absence or reduced CFTR function [6].

The combination of CFTR modulators ivacaftor and lumacaftor belongs to the drugs of pathogenetic therapy of CF. Ivacaftor, which is a *CFTR* potentiator, increases the activity of the protein delivered to the cell surface, which enhaces ion transport. Lumacaftor, which is a *CFTR* corrector, facilitates cellular processing and *CFTR* transportation that increase the amount of protein on the cell surface. The combination should lead to a sufficient level of protein on the cell surface and increase in its activity. Thus, these effects are intended to correct disorders caused by the F508del mutation. It is believed that if the combination has a sufficiently strong effect on *F508del*, then the presence of at least one such allele will be sufficient to obtain a significant clinical benefit [7].

Pathogenetic therapy is aimed to address the unmet needs of patients with cystic fibrosis. However, ethical concerns emerge due to excessively high prices of novel drugs for orphan diseases, making life-saving medicines inaccessible to patients [8]. Although high prices may be justified by the cost of new drug development and the limited market size in case of rare diseases, this circumstance is associated with a decreased adherence to treatment and leads to significant inequalities in access to the drugs. This violates the fundamental principle of medical ethics that consists in ensuring equality and justice in the provision of medical care. Like patients with more common diseases, patients with rare diseases benefit from lower prices for medicines due to appearance of generics. Generic drugs are about 80–85% cheaper than innovative ones, so their proper administration by clinical specialists can significantly reduce the cost of treating patients in need [9]. However, generic drugs will be affordable only if a sufficient number of drugs enter the market to ensure strong price competition. According to previous researches, introduction of one generic competitor to the market leads to a reduction in the price of drugs by about 10–15%. At the same time, in order to reduce the price by 50 percent or more, 4 or more generic drugs should be available on the market [10]. Drugs for the treatment of orphan diseases may not sufficiently compete with generics, since manufacturers of reproduced drugs often prefer drugs for the treatment of more common diseases. In this regard, development of as many generic drugs as possible to treat rare diseases makes a significant contribution to solving the ethical problem of limited patient access to therapy.

In addition, there is no need in an extensive program of preclinical and clinical trials (CT) similar to those conducted with respect to the original drug in order to register reproduced drugs. This approach is more ethical, as it reduces the number of subjects required for the study and duration of their participation in CT. Also, the reduced number of the conducted CT is justified from the perspective of economic efficiency. It ensures the maximum reduction of time required for registration and market launch of the drug. This makes it possible to ensure and maintain rapid access of patients to effective and safe therapy. It also reduces the risks associated with the possible termination of the original drug supply in the case of foreign manufacturers.

GP30511 tested in this study belongs to the reproduced drug (generics) containing ivacaftor and lumacaftor as active pharmaceutical substances. Today, patients and representatives of the medical community have prejudices about the lower effectiveness and safety of generic drugs in relation to original ones, and manufacturing companies sometimes use unethical ways to promote original drugs on the market. Despite this, the reproduced medicines can help meet existing medical needs by increasing the availability of drugs, which is correct from an ethical point of view [11, 12]. Increased access to effective and safe medicines will lead to an increase in the number of patients receiving appropriate treatment, earlier initiation of therapy in accordance with clinical recommendations, and a more reliable continuity of treatment.

The aim of this study was to investigate the comparative pharmacokinetics and bioequivalence of drugs containing ivacaftor and lumacaftor in healthy volunteers. Additionally, safety and tolerability of the studied drugs were evaluated as part of the study.

Clinical research is necessary to develop medical knowledge and improve the quality of patient care. By publishing the results of clinical trials, researchers contribute to the collective understanding of treatment methods and the results of their application. This sharing of information allows other researchers to rely on the existing knowledge and improve the

overall standards of research and patient care. Publishing the results of clinical trials is an ethical imperative that supports development of medical science, promotes transparency and prioritizes patients safety and well-being.

PATIENTS AND METHODS

The study population

Since the main objective of this study was to study the pharmacokinetic parameters of the tested drugs in order to prove their bioequivalence, a homogeneous population of healthy volunteers was selected to ensure the experimental purity and to obtain the most reliable data. The study population included healthy male and female volunteers aged 18–45 years with a body mass index of 18.5–29.9 kg/m^2, who agreed to comply with adequate method of contraception and restrictions imposed by the study protocol. Compliance with the criteria was established based on the collection of a medical history, physical examination and instrumental and laboratory examinations, which included electrocardiography, complete blood count, biochemical blood assay, urinalysis and serological tests for hepatitis C (antibodies) and hepatitis B (surface antigen and antibodies), HIV (antibodies to HIV-1/2) and syphilis (antibodies to *Treponema pallidum*). Also, all subjects underwent tests for pregnancy (for female participants), alcohol, cotinine, drug use and abuse of potent medicinal substances. During their stay at the research center, the volunteers had a monotonous diet. No strenuous activities, nicotine-containing products, medicines and bioactive additives, vitamins, foods and beverages that can affect metabolism were allowed during the entire study period. Before being included in the study, all subjects were explained all the restrictions imposed by the study and their rights, the volunteers were familiarized with the information sheet of the study subject and signed an informed consent form.

Investigational drugs

The investigational drug GP30511, containing ivacaftor and lumacaftor in the dose of 125 and 200 mg consequently as film-coated tablets, was produced by GEROPHARM LLC, Russia. The reference drug was the same dose of Orkambi®, produced by Vertex Pharmaceuticals Limited, Ireland. The investigational drugs were taken orally by subjects at a dose of 250+400 mg (2 film-coated tablets each) after a standardized high-calorie breakfast with 200 ml of still water at room temperature. Administration of the investigational drugs at the indicated doses is safe for subjects, does not exceed the maximum single and therapeutic doses and allows to provide the concentrations of ivacaftor and lumacaftor necessary for assessment of pharmacokinetic profiles with a minimal risk for healthy volunteers. This correlates with the literature data on already conducted studies of the combination and does not contradict the instructions for medical use of this drug [13].

Trial design

The bioequivalence study was an open-label, randomized, 2-period crossover study involving a single intake of the drug in each period (test or reference drug) in fed conditions. The study was conducted in one research center (Clinical Hospital No. 3, Yaroslavl). After hospitalization of the subjects and before the first administration of the drug, randomization was performed using the IWRS electronic system. The subjects were randomized into two groups: group 1 (TR) received the tested drug during the 1st period of the study and the reference drug during the 2nd; group 2 (RT) received the reference drug during the 1st period and the tested one during the 2nd period.

All hospitalization procedures were identical in all study periods. Hospitalization of the subjects started approximately 12 hours before each drug intake and lasted approximately 36 hours. After hospitalization, the researchers collected complaints, the subjects were interviewed to ensure compliance with the limitations of the study, a physical examination and assessment of vital signs were performed, alcohol breath tests were performed using an alcometer, drug and cotinine tests in urine were done using test strips, female volunteers also had a pregnancy test. On the day of hospitalization, subjects had a standard dinner according to the hospital's meal schedule followed by a restriction of the food intake. On the day of the drug administration, the volunteers were given a high-calorie breakfast, which they had to eat completely. The next meal was no earlier than 6 hours later. Before blood sample collection, vital signs were evaluated at –10 min and an intravenous peripheral catheter was placed in the ulnar vein to take blood samples for up to 12 hours after taking the drug, inclusive, with blood sampling at subsequent time points by direct venipuncture. The subject's hospitalization was completed following blood sampling at 24 hours after the drug was administered. Subsequently, the subjects were invited to outpatient visits at 48 and 72 hours after taking the investigational drug. During the outpatient visit, blood samples were taken for a biochemical blood test 72 hours after taking the drug in period 1. In the 2nd period of the study, a blood sample was taken for clinical and biochemical blood analysis and a urine sample was taken for urinalysis 72 hours after administration of the drug during the outpatient visit. Throughout the study, safety parameters were evaluated and adverse events were recorded.

The washout period in this study was 14 days, during it, the subjects continued to comply with all the limitations of the study. The total duration of this study was no more than 36 days for each volunteer.

Study endpoints

The pharmacokinetic parameters were evaluated in accordance with the purpose of the study. The total area under the plasma concentration of active drug -time curve (AUC) from zero to the collection of the last blood sample with the determined concentration of active substances of drugs at time point t (AUC_{0-t}) and the maximum observed concentration of active substances in the blood plasma of subjects during the observation period (C_{max}) were selected as the primary pharmacokinetic endpoints. Bioequivalence was assessed based on the data obtained.

Assessment of pharmacokinetic parameters

To assess the pharmacokinetic parameters during the study, blood samples were collected from subjects at 21 point in each period: –10 min predose and at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours, 3 hours 30 minutes, 4 hours, 4 hours 30 minutes, 5 hours, 5 hours 30 minutes, 6 hours, 8hours, 10 hours, 12 hours, 24 hours, 48 hours and 72 hours postdose.

Quantative determination of the concentrations of the active substances of the investigational drugs in blood plasma was performed using high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) according to a developed and validated technique. Validation was performed in accordance with the OECD, the Principles of Good Laboratory Practice (GLP), national and international standards. Validation was carried out according to the main characteristics of the technique: the degree of extraction of compounds from plasma, the matrix effect, the Lower Limit of Quantification (LLQ), calibration curves, precision and accuracy, selectivity, stability of compounds and sample transfer.

Safety assessment

The safety parameters were evaluated from the moment of the investigational drug first intake until participation in the study was completed. The assessment was carried out according to the occurrence and dynamics of adverse events, registered on the basis of complaints from subjects, according to physical examination, vital signs (blood pressure, heart rate, RR and body temperature) and laboratory and instrumental methods (complete blood count and biochemical blood tests, urinalysis and electrocardiography).

Statistical analysis

After completion of the study, the pharmacokinetic parameters were evaluated. The drugs were considered bioequivalent if 90% of the CI of the geometric mean AUC and C_{max} for both active substances were in the range of 80–125%.

The data analysis was performed using R Statistical Software (v 4.2.2). Statistical analysis of the main PK parameters was performed assuming their lognormal distribution. After the logarithmic transformation, an analysis of variance (ANOVA) was performed for the parameters AUC_{0-t} and C_{max} of the active substances of the investigational drugs. Descriptive statistics were calculated for primary and secondary pharmacokinetic parameters, as well as for safety parameters. To assess comparability, a PP population was analyzed, which included all volunteers who completed two study periods in accordance with the protocol. The safety assessment was carried out on the SAF population, which included all volunteers who received at least one dose of the drug.

THE RESULTS OF THE STUDY

Demographic data

A total of 60 subjects, TR (n = 30) and RT (n = 30), were included and randomized in the study. All participants completed the study in accordance with the protocol and were included in PP population. Not a single subject dropped out of the clinical part of the study. No serious deviations from the study protocol were observed (Fig. 1). The baseline characteristics of the study participants are presented in Table 1.

Pharmacokinetics

The analysis of pharmacokinetic data was carried out on the PP population. The obtained data on pharmacokinetic parameters for the investigational drugs are presented in Table 2. No significant differences were found between the tested and the reference drugs. A graphical representation of these concentrations of ivacaftor and lumacaftor demonstrates the matching shapes of the averaged pharmacokinetic profiles of the tested drug and the reference drug (Fig. 2, 3).

The results of the evaluation of the ratio of geometric mean pharmacokinetic parameters AUC_{0-t}, C_{max} of velpatasvir and sofosbuvir of the studied drugs and 90% CI for these ratios are presented in Tables 3 and 4. All parameters fell within the specified bioequivalence limits.

Safety

No adverse events were reported during the clinical trial.

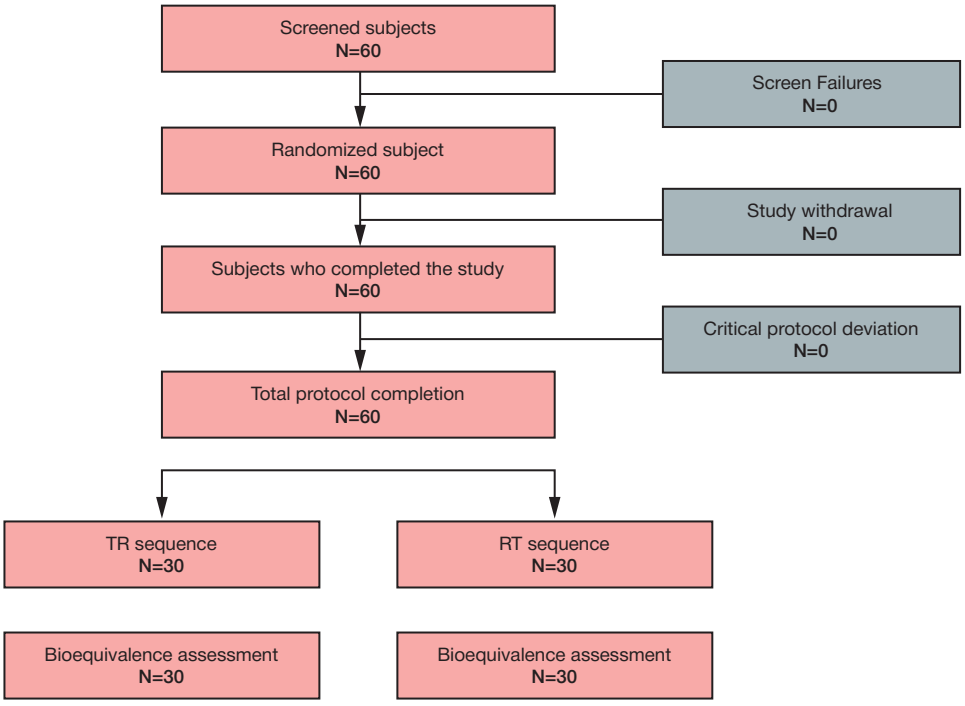

Fig. 1. Flow diagram of the distribution of subjects in a clinical trial

Table 1. Baseline characteristics of the study participants

Parameter		N=60
		Subject (% of N)/mean ± SD
Age, years		34.7±6.6
Gender	Male	28 (46.7)
	Female	32 (53.3)
Race (Caucasian)		60 (100)
BMI, kg/m^2		24.0±1.8
Weight, kg		70.4±8.6
Height, cm		170.8±6.0
Smoking – yes – no – history of smoking		– 0 – 60 (100) – 0
Alcohol – yes – no history of alcohol intake		– 8 (13.3) – 52 (86.7) – 0

Note: BMI is for body mass index, SD is for a standard deviation, N is for the number of randomized subjects.

Table 2. The obtained pharmacokinetic parameters after taking the tested and reference drug (N = 60)

Parameter	Ivakaftor			Parameter	Lumakaftor		
	The tested drug (mean ± SD)	The reference drug (mean ± SD)	The geometric mean ratios (90% CI)		The tested drug (mean ± SD)	The reference drug (mean ± SD)	The geometric mean ratios (90% CI)
AUC_{0-T} (ng/ml)/h	15415 ± 4359	15631 ± 4932	1.00	AUC_{0-T} (ng/ml)/h	392 ± 105	389 ± 99	1.00
C_{max} ng/ml	1575 ± 384	1609 ± 402	0.98	C_{max} mcg/ml	22 ± 3.5	22 ± 3.1	1.00
$AUC_{0-\infty}$ (ng/ml)/h	15602 ± 4386	15819 ± 4962	1.00	$AUC_{0-\infty}$ (μg/ml)/h	472 ± 168	463 ± 153	1.01
t_{max}, h	3.1 ± 0.9	3.1 ± 0.8	1.01	t_{max}, h	3.1 ± 1.0	3.1 ± 0.9	1.00
t1/2, h	8.3 ± 2.0	8.1 ± 2.0	1.02	$t_{1/2}$, h	27.6 ± 9.7	27.3 ± 8.6	1.00

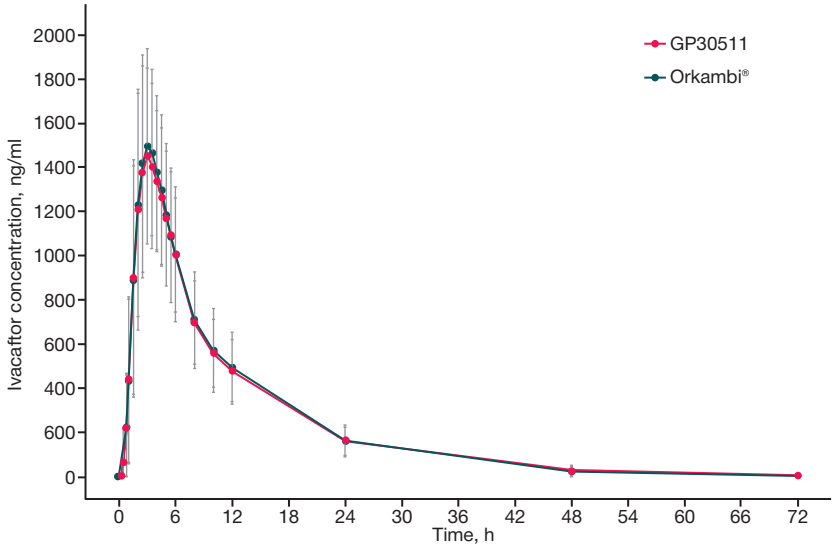

Fig. 2. Averaged pharmacokinetic profiles of ivacaftor in linear coordinates (mean ± SD, N = 60)

DISCUSSION OF THE RESULTS

Lumacaftor and ivacaftor are oral bioavailable peroral CFTR modulators, and their combination is the first drug combining a CFTR corrector and a potentiator. The lumacaftor-ivacaftor combination was developed for the treatment of patients with cystic fibrosis (CF) homozygous for the f508del-CFTR mutation [14]. Lumacaftor-ivacaftor is administered per os. It has shown effectiveness in improving the lung function and reducing the number of pulmonary exacerbations in patients with CF. Studies

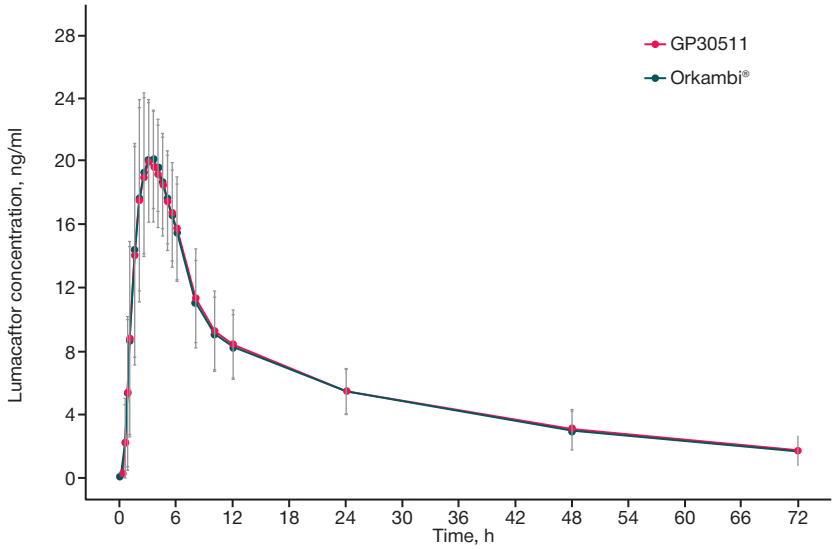

Fig. 3. Averaged pharmacokinetic profiles of lumacaftor in linear coordinates (mean ± SD, N = 60)

Table 3. The values of calculated confidence intervals for primary endpoints of ivacaftor pharmacokinetics (N = 60)

Parameter	The geometric mean ratio T/R	90% confidence interval		Estimated parameters for 90% CI	CV
		Lower limit	Upper limit		
AUC_{0-t}	1.00	95.92%	103.32%	80% — 125%	12.22%
C_{max}	0.98	94.71%	101.65%	80% — 125%	11.61%

Table 4. The value of calculated confidence intervals for primary endpoints of lumacaftor pharmacokinetics (N = 60)

Parameter	The geometric mean ratio T/R	90% confidence interval		Estimated parameters for 90% CI	CV
		Lower limit	Upper limit		
AUC_{0-t}	1.00	97.67%	103.08%	80% — 125%	8.84%
C_{max}	1.00	97.89%	102.35%	80% — 125%	7.31%

have shown that combination therapy gives a greater clinical effect compared with each of the drugs separately [15–17]. In addition, the combination of drugs can improve the condition of liver fibrosis in children and adolescents with CF, which indicates potential benefits in the treatment of CF-associated liver diseases [18].

According to the results of this study, the comparable pharmacokinetics and safety of the tested and reference drug were proved. The open nature of the study for volunteers and the researcher was chosen based on the fact that the primary pharmacokinetic points are sufficiently stable and resistant to the subjectivity of the study participants. In order to prove the bioequivalence of the studied drugs and to obtain the most reliable data, a population of healthy volunteers was chosen, since such a population is the most homogeneous one, which allows to reduce the intra-individual variability for bioequivalence research to the optimal level. This study was conducted in accordance with ethical principles designed to ensure the safety of the volunteers involved and to prevent any restriction of the rights of the subjects of the study. For this purpose, the study had a crossover design with the inclusion of the minimum number of subjects necessary to demonstrate the comparability of drugs, based on published literature data [19]. The dose of the drug, which was minimally sufficient for a reliable assessment of PK profiles, was also selected. It was acceptable from the perspective of safety and did not lead to the development of adverse events in the study.

60 healthy male and female volunteers were randomized and completed their participation in the studie according to the protocol, the analysis of pharmacokinetic parameters was carried out on the PP population, which included all randomized subjects. The results showed that the confidence intervals for the ratio of the geometric mean values of the pharmacokinetic parameters AUC_{0-t} and C_{max} of ivacaftor and lumacaftor in the PP population fell within the established acceptance limits of bioequivalence. Thus, this study made it possible to prove the bioequivalence of the studied drugs in a short time and in compliance with all requirements to ensure the safety of CT subjects for subsequent registration of GP30511.

CONCLUSIONS

Thus, based on the results of this study of GP30511 (GEROPHARM LLC) and Orkambi® (Vertex Pharmaceuticals Limited, Ireland), it can be concluded that the drugs are bioequivalent and have similar safety profiles. Entering the generic drug market will increase the availability of the combination of ivacaftor and lumacaftor for many patients with cystic fibrosis, which, in turn, will allow more effective management of the disease and improve patient survival. The implementation of GP30511 is an important step towards ensuring equal access of patients to modern treatment.

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MEDICAL REHABILITATION: ETHICAL AND LEGAL ISSUE RESEARCH

Pleshchev IE[1] ✉, Shkrebko AN[1], Kostrov SA[1], Ivashkovskaya AV[2], Savgachev VV[1], Efremov KN[1], Shishkin AA[3]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Yaroslavl Demidov PG State University, Yaroslavl, Russia

[3] Pirogov Russian National Research Medical University, Moscow, Russia

Medical rehabilitation is currently in an active phase of its development. This relevant area of domestic medicine is essential for human health. It helps patients recover from long-term illnesses, effects of injuries and diseases of the musculoskeletal system, peripheral nervous system and has a huge impact on the prognosis and outcome of treatment in general. This publication provides a comprehensive analysis of the ethical aspects of medical rehabilitation with an emphasis on legal definitions in medicine, which will improve understanding and regulation of relationship between rehabilitation, prevention and treatment. The research includes the study of domestic and international regulatory legal acts concerning medical rehabilitation, history of the specialty, the formulations that laid the foundation for the concept further development, consolidating an integrated approach to the issue of medical rehabilitation, as well as review of the problem-associated scientific papers. Explaining the principles of medical rehabilitation will help doctors avoid legal risks associated with their professional activity and serve as a guideline for taking ethically sound decisions in difficult clinical situations, whereas patients will get a full picture of their rights within the framework of medical rehabilitation.

Keywords: rehabilitation, humanism, medical education, medical ethics, medical law, treatment

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✉ **Correspondence should be addressed:** Igor E Pleshchev
Revolyutsionnaya str., 5, Yaroslavl, 150000, Russia; doctor.pleshyov@gmail.com

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МЕДИЦИНСКАЯ РЕАБИЛИТАЦИЯ: ИССЛЕДОВАНИЕ ПРОБЛЕМ ЭТИЧЕСКОГО И ПРАВОВОГО ХАРАКТЕРА

И. Е. Плещёв[1] ✉, А. Н. Шкребко[1], С. А. Костров[1], А. В. Ивашковская[2], В. В. Савгачев[1], К. Н. Ефремов[1], А. А. Шишкин[3]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославский государственный университет им. П. Г. Демидова, Ярославль, Россия

[3] Российский национальный исследовательский медицинский университет им. Н. И. Пирогова, Москва, Россия

В настоящее время медицинская реабилитация находится в активной фазе своего развития и является актуальным направлением отечественной медицины, очень значимым для здоровья человека. Она помогает пациентам восстановиться после длительной болезни, последствий травм и заболеваний опорно-двигательного аппарата, периферической нервной системы и оказывает огромное влияние на прогноз и результат лечения в целом. Данная публикация представляет собой комплексный анализ этических аспектов медицинской реабилитации с акцентом на правовые дефиниции в медицине, что позволит улучшить понимание и регулирование взаимосвязей между реабилитацией, профилактикой и лечением. Исследование включает в себя изучение отечественных и международных нормативно-правовых актов, касающихся медицинской реабилитации, историю возникновения специальности, формулировок, заложивших фундамент для дальнейшего развития концепции, закрепляя комплексный подход к вопросу медицинской реабилитации, а также научных работ, посвященных данной проблеме. Разъяснение принципов медицинской реабилитации поможет врачам избежать правовых рисков, связанных с их профессиональной деятельностью и послужит ориентиром для принятия этически обоснованных решений в сложных клинических ситуациях, а пациенты получат наиболее полное представление о своих правах в рамках медицинской реабилитации.

Ключевые слова: реабилитация, гуманизм, медицинское образование, врачебная этика, медицинское право, лечение

Вклад авторов: И. Е. Плещёв, С. А. Костров — концепция и дизайн исследования, ответственность за целостность всех частей статьи, редактирование; А. Н. Шкребко, А. В. Ивашковская — написание текста, редактирование; В. В. Савгачев — концепция и дизайн исследования, редактирование; К. Н. Ефремов, А. А. Шишкин — ответственность за целостность всех частей статьи, редактирование.

✉ **Для корреспонденции:** Игорь Евгеньевич Плещёв
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; doctor.pleshyov@gmail.com

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The purpose of the study is to analyze in detail and identify the issues related to the legal and ethical aspects of medical rehabilitation. Differentiation between such concepts as ‘medical rehabilitation’ and ‘treatment’ promotes a more accurate and effective understanding of medical rehabilitation issues and allows to avoid legal ambiguities.

Explaining the concept of medical rehabilitation will help doctors avoid legal risks associated with their professional activity, and provide them with landmarks for making ethically sound decisions in complex clinical situations. Understanding modern legal and ethical standards will improve the quality of medical care, which in turn will increase patients’ trust in medical institutions and specialists.

Patients will receive more complete and accurate information about their rights and opportunities within the framework of medical rehabilitation. This will allow them to make informed decisions about their health and treatment.

LEGAL ASPECTS OF MEDICAL REHABILITATION

In 1946, at the Congress on the rehabilitation of patients with tuberculosis in Washington (USA), one of the first official definitions of 'medical rehabilitation' was proposed. It was defined as a multidimensional process in the form of 'restoration of the physical and spiritual strength of the victim, as well as of the victim's professional skills'. This definition laid the foundation for further development of the concept, strengthening an integrated approach to the issue [1].

Over the past time, the concept of 'medical rehabilitation' has undergone numerous changes and clarifications. In 1980, the World Health Organization (WHO) formulated a widely used definition, where medical rehabilitation is understood as an active process with the goal of achieving complete restoration of functions impaired due to a disease or an injury, and if this is not possible, of developing compensatory and replacement devices (functions) [2, 3]. Most publications on this topic, both at the Russian and international levels, are based on this conceptual definition. The formulation developed by the WHO also highlights the need for an integrated approach that promotes a more complete and comprehensive recovery of patients. The active role of the patient in rehabilitation, development and implementation of new rehabilitation programs, increasing patient motivation and improving rehabilitation results is emphasized. The developed compensatory and substitution mechanisms allow patients to adapt to new living conditions and be as much independent as possible.

The above definition of medical rehabilitation can be applied mainly in specialized medical literature, where it significantly differs from the interpretations presented in commonly used explanatory dictionaries. This is due to the fact that the WHO definition is highly specialized and can be used within the professional medical community only. At the same time, definitions in explanatory dictionaries are often more generalized and even more simplified, which makes them accessible to a wide audience.

For example, the Explanatory Dictionary of the Russian language, edited by Ozhegov SI and Shvedova NYu (1992), considers medical rehabilitation in a rather narrow sense, focusing mainly on eliminating the consequences of severe diseases or injuries [4]. In contrast, the definition presented in the Explanatory Dictionary of the Modern Russian Language (2013) reflects a broader and multifaceted approach to understanding medical rehabilitation and designates medical rehabilitation as a complex of medical, pedagogical, professional measures aimed at restoring (or compensating) impaired bodily functions and labor ability of patients and the disabled [5].

Another example is the Dictionary of Terms of the Ministry of Emergency Situations, in which medical rehabilitation is understood as a system of medical measures aimed at preventing decreased and lost labor ability, early restoration of impaired functions, prevention of complications and relapses of diseases, and early return to a professional activity [6]. In this case, the emphasis is made on the preventive manner of rehabilitation measures. This approach emphasizes that rehabilitation is required not only to restore lost functions, but also to prevent further deterioration of health and preserve the labor potential of patients.

As the term 'medical rehabilitation' is interpreted in specialized medical literature and commonly used explanatory dictionaries in a different way, representatives of the professional medical community have repeatedly raised the issue of the need to develop a unified definition of this concept and its consolidation in regulatory legal acts [7]. Such unification of terminology at the legislative level is considered as an important condition to eliminate legal uncertainty, ensure uniformity in law enforcement practice and create a reliable legal basis for the implementation of rehabilitation activities in the field of healthcare.

Though the concept of medical rehabilitation has been actively developed in the global medical practice and scientific literature, there has been no clear definition of this concept in the Russian legislation for a long time. The regulations adopted before 2003 used terms such as 'restorative treatment' and 'follow-up treatment', which only partially reflected the essence and content of the rehabilitation process.

Since 2003, the term 'restorative medicine' has appeared in regulatory legal acts, namely in Order of the Ministry of Health of the Russian Federation dated 07/01/2003 No. 297 'On rehabilitation doctor' and order of the Ministry of Health of the Russian Federation dated 03/9/2007 No. 156 'On the Procedure for organizing medical care in restorative medicine' [8, 9]. According to experts, the introduction of the term 'restorative medicine' has become an important step towards recognizing rehabilitation as an independent area of medical activity. However, this concept neither fully reflected all aspects of the rehabilitation process nor allowed for a clear distinction between rehabilitation and other types of medical care [10].

The situation changed in 2011 only, when the official definition of medical rehabilitation was fixed in Federal Law No. 323-FZ dated 11/21/2011 'On the Basics of Public Health Protection in the Russian Federation' [11].

In accordance with Part 1 of Article 40 of the said Federal Law, it was determined that medical rehabilitation is a set of medical and psychological measures aimed at the complete or partial restoration of the impaired and (or) compensation for the lost functions of the affected organ or body system, maintaining body functions during the completion of an acutely developed pathological process or exacerbation of a chronic pathological process in the body, as well as for the prevention, early diagnosis and correction of possible violations of the functions of damaged organs or body systems, prevention and reduction of possible disability, improvement of quality of life, preservation of the patients' working capacity and their social integration into society.

An official definition of medical rehabilitation has become an important milestone in the development of this medical specialty [12]. The consolidation of the legal definition at the federal law level indicates that the state has recognized the importance of rehabilitation in the healthcare system and the need to create an appropriate regulatory framework to allow its functioning.

However, this formulation does not allow for a sufficiently clear differentiation between rehabilitation measures and other types of medical care, such as treatment and prevention. In addition, the wording used in the law does not fully take into account the multidimensional nature of the rehabilitation process, which includes not only medical and psychological, but also professional and social components.

As such legal concepts as 'treatment' and 'medical rehabilitation' are interpreted in an ambiguous way, it complicates not only the regulation of medical activity as such, but also becomes the subject of discussion when solving the problem of insurance and financing. The answer to the question about which types of rehabilitation services should be covered by insurance or government programs may depend on whether rehabilitation is qualified as part of the treatment process or as a separate category of medical services.

Table. The main differences in interpretation of medical terms

Comparison criterion	Treatment	Rehabilitation	Prevention
Goal	It is aimed at eliminating the causes and symptoms of the disease.	It is aimed at restoring body functions and adapting to life after illness.	It is aimed at preventing diseases and promoting health.
Time perspective	It focuses on the present and current state of health.	It is focused on the future, restoration and forecasting of working capacity and quality of life.	It prevents future diseases and improves overall health.
Patient participation	The patient may be a passive participant.	It requires active participation and involvement of the patient in the recovery process.	Both medical professionals and the patient (for example, vaccination, healthy lifestyle) need to be active.
Diagnostic base	It is based on the nosological and syndromological diagnosis.	It is based on a functional diagnosis by assessing the degree of dysfunction and possibility of recovery.	It is based on assessment of risks and factors contributing to the development of diseases.
Examples	Medical treatment, surgical intervention.	Physiotherapy, speech therapy, adaptive physical education.	Vaccination, promotion of a healthy lifestyle, regular medical examinations.

Treatment is aimed at combating the disease and its causes. It includes diagnostics, appointment and implementation of therapeutic activities to eliminate or compensate for the disease. The treatment can be both active and passive. It does not always require active participation of the patient. It is focused on the present state of the body and manifestations of the disease. Medical rehabilitation (MR), in turn, is aimed at restoring body functions after a disease or injury. It includes a set of measures aimed at mobilizing the body's defense mechanisms, restoring lost functions and adapting to life with limitations, if any. Rehabilitation requires active participation of the patient and is focused on the future, returning to normal life and restoring the working capacity. While comparing overlapping medical definitions, it is necessary to consider the term 'medical prevention', which means a set of measures aimed at preventing development of diseases, reducing their spread among the population, as well as reducing or eliminating risk factors contributing to occurrence and development of pathological conditions.

In Table, the main criteria for differences in formulation of these established medical concepts are considered.

According to Resolution No. 291 dated 04/16/2012 [13] of Government of the Russian Federation and adopted substituting Resolution No. 852 dated 06/01/2021 [14], medical rehabilitation is a separate service, the implementation of which is subject to licensing. The procedure for organizing this activity is regulated by Orders of the Ministry of Health of the Russian Federation dated 10/23/2019 No. 878н and 07/31/2020 No. 788н in relation to children and adults respectively [15, 16]. These regulatory legal acts indicate that medical rehabilitation is carried out in medical organizations licensed for medical activities, including work (services) on medical rehabilitation, and they also differentiate between early, late and supportive rehabilitation.

An important change was that MR is now carried out at all stages by a multidisciplinary rehabilitation team (MDRT), which carries out its activities in accordance with the approved procedure, and MDRT functions under the guidance of an expert, physical and rehabilitation medicine/medical rehabilitation doctor.

It should be noted that these regulatory and legal provisions have made the tasks and scope of activities of specialized institutions related to medical rehabilitation clearer and more specific, and have become an impetus for further rehabilitation development.

ETHICAL ASPECTS

The foundation for the consideration of ethical issues in medicine includes four basic principles of medical ethics such as respect for patient autonomy, integrity, charity and justice.

Dilemmas arise due to differences in the interpretation and application of terms in different contexts, which can lead to conflicts between the interests of patients, medical professionals and the healthcare system as a whole.

Disease prevention addresses issues of mandatory vaccination, screening and lifestyle. Here, ethical dilemmas are often related to the balance between individual freedom and public good, so, for example, vaccination can be taken as a violation of autonomy, though it also protects public health. Vaccination against COVID-19 can serve as an example. On the one hand, it saves lives and prevents the spread of the virus, and, on the other hand, people expressed concerns about the rapid development of vaccines and potential side effects.

In the context of treatment, an ethical choice may arise in a situation when interests of the patient conflict with medical standards and recommendations, or when the doctor mainly focuses on the research process in which the patient participates. It is important to concentrate on the patient's well-being trying not to ignore his interests.

The legal definition of 'treatment' implies active actions aimed to eliminate or alleviate the symptoms of the disease. However, doctors may face a situation where the patient refuses the proposed treatment, even if it can save his life. There is a dilemma between respecting the patient's autonomy and desire to act in the patient's best interests.

In the field of rehabilitation, ethical issues are often related to availability and necessity of services provided to the patient by a medical institution. Rehabilitation is aimed at bringing the patient to life, which requires an MR specialist to pay attention not only to the physical, but also to the psychological state of the patient. It is important to maintain a balance between using technologies to improve the quality of rehabilitation and maintaining a personal contact with the patient to ensure his motivation and participation in the recovery process, which is especially important when rehabilitation efforts meet limited resources and the need for rational allocation hereof.

One of the main ethical dilemmas associated herewith is the prioritization and allocation of resources between treatment and rehabilitation. When healthcare system resources are limited, we can invest either in expensive medical procedures that

can prolong the patient's life, or in rehabilitation services that improve the patient's quality of life.

The question of using the 'medical necessity' term in the context of justifying the provision of rehabilitation equipment is raised. Ethical considerations influence the definition of the concept of medical necessity, since insurance companies can cover the cost of medical equipment only if it is necessary to use it for carrying out medical and diagnostic measures. This underlines the importance of provision of a clear and objective definition of medical necessity at the legislative level, so that specialized rehabilitation equipment could be as accessible as possible to those in need of it.

Sometimes, after successful high-quality treatment, patients are discharged from medical institutions in an environment that goes against the needs of rehabilitation. Often, the financial and household constraints of the patient or his family, as well as the lack of places in specialized institutions, do not allow for proper care. Discharge to unsuitable conditions may negatively affect health and subsequent rehabilitation of the patient. It is necessary to increase the availability of rehabilitation and social services, improve coordination between medical and social services, and involve patients and their families in planning and conducting rehabilitation activities.

Coding and billing conflicts pose a serious ethical dilemma. On the one hand, medical professionals strive to provide patients with the best possible care and the necessary amount of rehabilitation services. On the other hand, they have to work within the limits imposed by the health insurance system, the institution's budget and administrative rules. The need to comply with limited number and duration of rehabilitation procedures covered by insurance, pressure from the administration to reduce costs and increase profits, the complexity of the rules for coding services, which do not always show the real cost of time and effort, significantly complicate the work of a doctor who has to balance between these conflicting requirements. As a result, medical professionals may face difficult choices. For example, they have to divide one long procedure into several short sessions in order to fit into the limits, or to choose a treatment method that is not the most effective for the patient, but can be considered more 'profitable' from the point of view of coding. Such decisions can be in conflict with professional ethics and personal values. It is necessary to improve the coding and payment system for rehabilitation services, taking into account real labor costs, develop ethical guidelines for resolving conflicts between financial and clinical priorities, and train how to communicate with the administration effectively to defend the interests of patients.

Interdisciplinary cooperation plays an important role in treatment and care for patients in the context of medical rehabilitation and ethics. It includes the work of doctors, nursing staff, psychologists and other specialists as a single team with a common goal, which consists in returning the patient to a full life. This requires each team member to be willing to work together, open to share knowledge, and respect the professional contributions of colleagues. Effective interaction between doctors of different specialties is the main criterion of a patient-oriented approach, contributing to the creation of an integrated treatment and rehabilitation plan that takes into account all aspects of the patient's health and well-being.

Respectful attitude helps to create an atmosphere of trust and open communication, which allows team members to freely share their ideas, experiences and suggestions for improving treatment and rehabilitation processes. All actions and decisions of the interdisciplinary team should be aimed at increasing the benefits for the patient and minimizing possible risks, which implies a willingness to find a joint solution in case of disagreement. It is necessary to develop internal protocols and procedures governing interaction between specialists, conduct joint consultations, use common standards and treatment protocols, and introduce information technologies to facilitate communication and dynamic exchange of patient-related data between specialists.

CONCLUSION

Legal norms in medicine are often based on ethical principles. However, there are differences between these two areas. Law is a system of mandatory rules, the violation of which entails legal responsibility, while ethics is focused on the moral aspects of activity and is often advisory in nature.

The legal definitions of 'treatment' and 'rehabilitation' carry important ethical aspects related to the rights of patients, duties of medical professionals and social values. It is important that the legal framework maintains high ethical standards in medical practice, while ensuring adaptation to changes in medical technology and in public expectations of medical care. This requires an ongoing dialogue between medical professionals, lawyers, ethicists, and society as a whole to ensure that legal definitions and practices reflect and protect core ethical principles and values.

An open discussion of these problems by the professional community will help to find ethically acceptable solutions and better cope with moral distress, while being committed to the duty to patients.

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ISLANDS OF MERCY. RUSSIAN DOCTORS DURING MILITARY OPERATIONS IN THE NORTH CAUCASUS IN THE 1990s AND EARLY 2000s

Tumakov DV ✉

Yaroslavl State Medical University, Yaroslavl, Russia.

At the turn of the XX–XXI centuries, Russia had to conduct active military operations twice to suppress the hotbed of separatism, crime and terrorism in the North Caucasus. Serious military medicine forces had to be involved. Meanwhile, the participation of medical professionals in two Chechen operations is still on the periphery of attention of domestic researchers. In the 1990s and early 2000s, the Russian mass media wrote that military doctors were helping wounded and sick servicemen of the federal troops directly on the front line and in rear hospitals, often informed the general public about maintaining the mental health of recent front-line soldiers, and also never ignored the assistance to the civilian population (women, the elderly, children) of the Chechen Republic. Some press publications described the most successful and complex operations performed by Russian military surgeons. In many publications of those years, you can also find reports about the doctors who distinguished themselves the most during the active hostilities and were awarded high state awards, including the Gold Star of the Hero of the Russian Federation. The practical activities of Russian doctors in the North Caucasus in the 1990s and early 2000s resulted not only in the saving of the lives of the vast majority of wounded soldiers, but also in restoration of the Chechen health system, prevention of epidemics and successful fight against numerous infectious diseases.

Keywords: military doctors, North Caucasus, Chechnya, Russia, military operations, army

✉ **Correspondence should be addressed:** Denis V. Tumakov
Revolyutsionnaya str., 5, Yaroslavl, 150000, Russia; denistumakov@yandex.ru

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ОСТРОВКИ МИЛОСЕРДИЯ. РОССИЙСКИЕ МЕДИКИ ВО ВРЕМЯ ВОЕННЫХ ДЕЙСТВИЙ НА СЕВЕРНОМ КАВКАЗЕ В 1990 — НАЧАЛЕ 2000-х гг.

Д. В. Тумаков ✉

Ярославский государственный медицинский университет, Ярославль, Россия

На рубеже XX–XXI вв. России дважды пришлось вести активные боевые действия для подавления очага сепаратизма, криминала и терроризма на Северном Кавказе. Они потребовали привлечения серьезных сил военной медицины. Между тем участие медицинских работников в двух чеченских операциях и по сей день нередко остается на периферии внимания отечественных исследователей. Российские масс-медиа 1990 — начала 2000-х гг. писали об участии военных врачей в помощи раненым и больным военнослужащим группировки федеральных войск непосредственно на передовой и в тыловых госпиталях, нередко информировали широкую общественность о поддержании душевного здоровья недавних фронтовиков, а также не оставляли без внимания помощь гражданскому населению (женщины, старики, дети) Чеченской республики. В некоторых публикациях сообщалось о наиболее успешных и сложных операциях, проведенных российскими военными хирургами. На страницах многих средств массовой информации тех лет также можно обнаружить репортажи о наиболее отличившихся во время активных боевых действий врачах, удостоенных высоких государственных наград, включая Золотую Звезду Героя Российской Федерации. Итогом практической деятельности российских медиков на Северном Кавказе в 1990-е и начале 2000-х гг. стало не только спасение жизней подавляющего большинства раненых бойцов, но и восстановление системы здравоохранения Чечни, предотвращение эпидемий и успешная борьба с многочисленными инфекционными заболеваниями.

Ключевые слова: военные медики, Северный Кавказ, Чечня, Россия, боевые действия, армия

✉ **Для корреспонденции:** Денис Васильевич Тумаков
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; denistumakov@yandex.ru

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In the 1990s and 2000s, post-Soviet Russia faced a permanent crisis in the North Caucasus region. Emergency measures were required from the state to eliminate the hotbed of separatism, crime, and then the terrorist threat. In those years, a turbulent situation has developed in many national republics of the Caucasus, but in order to restore constitutional legality, law and order in the Chechen Republic, the federal Center conducted two heavy military operations in 1994–1996 and 1999–2009. Historians believe that none of the 'hot spots' of the USSR and the post-Soviet space at the turn of the 1980s and 1990s required the state to use such large forces and means [1]. Their causes, the course of military operations, and even assessments in the Russian society of that time have repeatedly been the subject of study by domestic researchers in recent years, but such important aspects of the problem as participation of Russian military doctors in military operations in the Caucasus and their role in resolving this conflict are still relatively poorly studied by domestic researchers. This publication is intended to at least partially fill in this gap. The most important source for it is the Russian periodical press of the turn of the XX–XXI centuries, which includes both professional (Medical Newspaper) and many socio-political publications (Segodnya, Ogonyok, Arguments and Facts, Independent Military Review).

Trying to emphasize the scope of achievements of Russian military medicine in the Chechen campaigns, the authors of publications in the Medical Gazette regularly cited certain high quantitative indicators of the work of doctors. For example, in the midst of the bloody battles for Grozny in August 1996, the publication reported that a transport plane from Chechnya arrived at Volgograd airport, carrying 80 wounded servicemen who had previously received primary medical care in the hospitals of Khankala and Vladikavkaz. 23 of them, who had abdominal, chest or multiple shrapnel wounds of soft tissues,

were in a serious condition, so 21 ambulance crews met the wounded at the airport. According to the newspaper correspondent Papyrin A, the flow of the wounded was slightly inferior to that observed in winter of 1995; all 485 beds in the military hospital of the Volgograd permanent post were occupied again, including 192 wounded from Chechnya [2]. Another article in the same issue of Medical Newspaper did not provide statistical data, but published photos of ITAR-TASS with the wounded in Grozny and reported their arrival first to Beslan airport (Republic of North Ossetia-Alania), and then to the North Caucasian Military District hospital in Rostov–on-Don [3].

We can find similar facts in the periodical press of the turn of the 1990s-2000s, which already narrated the events of the second Chechen campaign. Thus, the senior lecturer of the Department of military field surgery of the Military Medical Academy named after S. M. Kirov, colonel of the medical service Marchuk V recalled that when the federal troops advanced on Grozny and during the battles for the commanding heights above it in the autumn and winter of 1999, up to 70 wounded soldiers arrived at the hospital daily, and the maximum number was 156 people one day [4]. These estimates cited in an interview with the Independent Military Review (appendix to the Nezavisimaya Gazeta, one of the most authoritative and influential Russian publications of the post-Soviet period) were generally confirmed by an anonymous medical instructor of a motorized rifle company, according to whom an average of 5–6 servicemen died and 15 were injured per day at the height of the active hostilities [5]. At the same time, in 1999–2000, significant progress was observed in the work of doctors compared to the military commitment of 1994–1996: the evacuation of the wounded with the help of aviation was better organized, there were practically no problems with supply of the army with medicines, and almost all fighters were vaccinated before being sent to the Caucasus [4]. To transport the most seriously wounded to hospitals located in capitals, the federal group actively used AN-72 and Il-76 ambulance aircraft, with the intensive care unit and operating room being located on board the latter. The delivery time for such wounded soldiers from the battlefield to the hospital ward was 6 hours in average [4].

It is important that regular publications of major media about the attempts of the Russian medical community to overcome the severe consequences of active military operations in the North Caucasus in the 1990s and early 2000s were not impersonal. On the contrary, a significant role among them was played by relatively extensive materials about the most distinguished Russian military doctors who were awarded high state awards for feats in the Caucasus region. The most famous of them was the Hero of Russia, commander of the medical company of the 27th Brigade of Airborne Troops, Guard major of the medical service Belov AA, who participated in the capture of Grozny and Argun as part of the surgical medical center of the consolidated regiment in the first quarter of 1995. In the mass media of the mid-1990s, he was actually compared to front-line doctors of the Great Patriotic War era. So, in one of the notes in the Medical Gazette, published in 1996 on the eve of Victory Day, it was reported that Belov's grandfather was also a military doctor and died at the front in 1941 [6]. It is very noteworthy that apart from Belov VA, three other heroes of the same publication were doctors awarded the Gold Star of the Hero of the Soviet Union for rescuing wounded Red Army soldiers or partisans in 1941–1945.

A year and a half after the entry of federal troops into the rebellious republic and the beginning of large-scale hostilities, in an interview with the correspondent of the Medical Newspaper, reserve Colonel R. Chekmarev, Belov laconically recalled that during the storming of the Chechen capital at the beginning of the 1994–1996 campaign, 'days and nights were mixed for us. And the wounded kept coming' [7]. Then he together with his colleagues rescued hundreds of wounded Russian soldiers [6]. On the contrary, the capture by federal forces of the third largest city of Chechnya, Argun, on March 23, took the lives of 5 soldiers of a combined airborne regiment, and very few wounded were received at the medical center [7]. It should be noted that the above information about the losses of the federal group completely coincided not only with the official estimates of the army command, but also with those of the metropolitan journalists who were very critical about the military solution of the Chechen crisis [1].

In the same interview, Guards Major Belov emphasized the high professionalism and personal courage of his colleagues. Pugachev V, Lukonin V, Kirh A. Noskov R, Germanov V, Chaplygin A and Barinov B [7]. With reference to unnamed Russian soldiers, they were also provided a specific example of his work in the war zone. In winter of 1995, in Grozny, senior lieutenant of the medical service Leonenko E. came under fire from militants, barely got out of a burning armored personnel carrier, but fell into a sewer well and almost died, as Chechen separatists threw a hand grenade there. The seriously wounded medical officer was able to reach the place where the Russian troops were located only three days later. Leonenko was given primary care at the medical center and sent to the hospital, where he was diagnosed with 'contusion, multiple shrapnel wounds, and thermal burns [7]'. His further fate was unknown to Belov VA.

Russian doctors had to act in no less difficult circumstances during the second campaign in Chechnya. Comparing the two operations in the North Caucasus, military surgeon, Hero of Russia, Lieutenant Colonel of the medical service Milyutin IA considered the events of 1999–2000 to be a more difficult test due to frequent movements across the territory of the rebellious republic [4]. During the fighting in the Novolak district of Dagestan in September 1999, enemy snipers and mortars tracked the movement of medical workers and fired heavily at them. To avoid death or injury, it was necessary to use armored vehicles, which blocked the visibility of snipers and helped to pull wounded Russian servicemen from the battlefield [4]. According to the memoirs of the head of the surgical department of Vishnevsky A. Central Military Clinical Hospital, Lieutenant Colonel of the Medical Service Filippov AV, transfer to another location occurred about 1–2 times a week. Each time, the military field hospital was deployed from scratch, in the bleak steppe, with no electricity, water supply and communications around. According to the military doctor, his colleagues 'were mid leg deep in the mud', worked and lived in tents measuring 30 by 10 meters [8].

The main author of another large essay published on the pages of the Medical Newspaper in summer of 1996 was the head of the microsurgery department of the 3rd Central Clinical Military Hospital named after Vishnevsky A (the city of Krasnogorsk, Moscow region), Lieutenant Colonel of the Medical Service Kuzin VV. According to the author of the publication, journalist Golovenko A, the mentioned surgeon annually performed up to 200 complex operations, which resulted in recovery of even hopeless wounded. It is noteworthy that Golovenko himself was a witness to one of them. It lasted about 8 hours. He later told readers about the fate of some military personnel who became patients of the Krasnogorsk hospital. For example, the 18-year-old sergeant of the Russian army Semakin A, almost lost his right arm after being hit by a burst of a large-caliber machine gun in a battle with terrorists from S. Raduyev's gang in the Dagestan Pervomaiskoye village (January 1996). However, the military doctor Kuzin cut out the fibula from the shin and fixed it to the shoulder, which saved the fighter's limb. A veteran of the Afghan war and some hot spots in Transcaucasian countries, the foreman of the reconnaissance company Emelyanov Yu had

'his stomach… full of fragments' during the storming of Grozny in winter of 1995, as a result of a close shell explosion. However, the doctor cut out a thin muscle from the thigh and carefully applied a 'patch' to the stomach. Moreover, Kuzin was even able to transplant Yemelyanov's finger from his foot to his hand. The case of common soldier Kolomnin I was also mentioned in the article. He almost lost his right leg below the knee as a result of the explosion of his BMP on a radio-controlled land mine near Argun. The soldier also avoided amputation due to the highest professionalism of Kuzin, who transplanted a fibula with a muscle from the left leg to the soldier's right leg [9].

The central mass media promptly reported that doctors of some provincial military medical institutions also achieved notable professional results during the first Chechen campaign of 1994–1996. So, only 3 wounded servicemen died in the surgical department of the Volgograd Military Hospital during the capture of Grozny in winter of 1995, although two planes with wounded arrived daily from the Chechen capital to Volgograd airport, and 'soldiers, officers arrived directly with equipment, and machine guns, in burnt, dirty pea jackets' [10]. After the escalation of the situation in Grozny in spring of 1996, 90 more wounded and sick Russian servicemen were taken to the same hospital. The heroic work of doctors has not been ignored by the state and society. For successful professional activity, doctors Bryzgunov A, Asimov A, as well as the operating nurses Vasilyeva I and Sharai S were awarded government awards, and the lead surgeon Goncharov A even described own experience in his report at a meeting of the regional society of surgeons [10].

The example of the Volgograd Military Hospital was not the only one cited in the major media in those years. For example, in another issue of the Medical Gazette it was mentioned that the head of the department of traumatology of Inpatient military hospital No. 358 of the Volga Military District (the city of Samara) Colonel of the Medical Service Fedoseev MM, who served in Afghanistan in the 1980s, developed and implemented several operations into daily practice. They included plastic ligaments of a traumatically damaged knee joint and a dielectric insert into the Ilizarov apparatus, which reduced the time of fusion of limb fractures by more than a month. Moreover, as stated by a journalist of the Medical Gazette, no single case of death among wounded servicemen had been recorded in the department of traumatology of the Samara Hospital by summer of 1996 [11]. Meanwhile, during the first Chechen campaign, 1,900 wounded soldiers passed through the Samara hospital, with 120 of them staying in the intensive care unit [12].

Russian military doctors tried to save not only physical, but also mental health of their patients. In a large article in the Medical Newspaper, the famous military journalist Colonel Karpov BV mentioned the participant of the Great Patriotic War of 1941–1945, Candidate of medical sciences, psychotherapist Perevalov IP from the sanatorium of the Ministry of Internal Affairs in Kislovodsk (Stavropol Territory). During a year and a half of active hostilities in Chechnya, he and his colleagues provided a full 24-day course of treatment to more than 400 wounded officers and soldiers of the Airborne Forces, whereas other 100 soldiers obtained treatment within the 12-day program [13]. To do this, doctors at the resort had narzan baths, physical therapy, hydro, acupuncture and aromatherapy courses. They also attended a phytobar, a sauna and a swimming pool. However, as the author of the publication noted, the main indicator of highly effective treatment in Russia sanatorium were excerpts from letters of the vacationing Russian military themselves. N., a soldier of the Ministry of Internal Affairs of the Russian Federation, who had previously served in the 'hot spots' of Transcaucasia, expressed gratitude to Perevalov for having 'become different' after treatment in the sanatorium, that is, he felt the urgent need to continue life. In turn, Colonel V., a veteran of the war in Afghanistan, wrote that after Perevalov's rehabilitation, he 'returned to normal human life' and stopped alcohol abuse. It should be noted that the medical experience gained during the military operations in the North Caucasus was analyzed long before the formal end of this armed conflict. Thus, rehabilitation departments were created in sanatoriums and rest homes of the Ministry of Internal Affairs of Russia, and freelance military medical commissions were established directly in military units to refer front–line soldiers to rest, treatment and rehabilitation in a sanatorium. With the support of officers of the Military Medical Directorate of the Government Apparatus Perevalov IP was preparing a memo for participants of military conflicts [13].

Russian doctors provided assistance not only to wounded or sick servicemen and representatives of other law enforcement agencies, but also to the civilians of the Chechen Republic. In the above-mentioned interview with the Guards Major Belov VA it was claimed that residents of Grozny, especially the elderly, women and children, repeatedly became his patients. They were either receiving the necessary medicines or emergency assistance from army doctors for free. The military doctor recalled that in winter and early spring of 1995, he and his colleagues often gave their own combat rations to 'people who were starving, huddled in basements and tumble-down houses' [7]. His point of view was shared by Prokofieva N, the correspondent of the 'Ogonek' magazine that was popular in the late Soviet and post-Soviet years, who repeatedly visited Chechnya at the height of hostilities. In her opinion, largely thanks to the efforts of Russian military doctors in the republic during the war years, it was possible to prevent a repeat of the cholera outbreak; the fight against polio, plague, diphtheria, anthrax, dysentery and hepatitis was successful. Thanks to the efforts of the Deputy Chairman of the State Committee for Sanitary and Epidemiological Supervision Onishchenko GG, the restoration of the sanitary and epidemiological service destroyed during the years of the separatist regime began in Chechnya [14].

A similar point of view about the relationship between doctors and Chechen civilians was shortly expressed before the end of hostilities in 1996 by director of Protection All-Russian Center for Disaster Medicine, Major General of the Medical Service, Goncharov SF. According to him, there was a 'very good atmosphere, a friendly atmosphere' around the hospital in the village of Staraya Sunzha in the suburbs of Grozny in 1994–1996, because the local population 'helped the doctors very well'. For the residents of Chechnya, the very existence of a medical facility was something like a barometer. They regularly asked the doctors if the hospital would leave and whether they need to leave the settlement as well. At that time, the team of the Zashchita Hospital included 23 highly qualified specialists such as neurosurgeons, traumatologists, pediatric surgeons, anesthesiologists from leading clinics in Moscow [15]. The importance of their assistance to civilians could not be overestimated. During the battles for Grozny in August 1996, over 370 people turned to them for help, including 117 wounded [15]. As Professor Goncharov reported, his subordinates provided support to numerous women who received penetrating wounds to the thoracic, abdominal and cranial cavities, and the vast majority of patients were rescued and later evacuated to hospitals in Vladikavkaz, Mozdok and the Znamenskoye district center. Russian doctors failed to save only two seriously injured people [15].

Another important event directly participated by Russian doctors during the military operations in the North Caucasus was the 'Frontline Children of Chechnya' charitable social and medical program, launched in 1995 by the Russian Children's Fund (RDF). Its main goal was to organize the rehabilitation and treatment of disabled children in the new 'hot spot' of the

post-Soviet space. In more than a year, up to 250 Chechen children were sent to medical institutions in the neighboring national republics of the North Caucasus (Ingushetia, Dagestan, North Ossetia-Alania), and another 22 children were sent to hospitals in Moscow. Obviously, these indicators were a drop in the bucket as only in the first weeks of March 1996 and only in Grozny, the RDF staff identified more than 70 more children and adolescents who could not be cured in Chechnya and had to be urgently taken to special clinics in large cities of the country for rehabilitation. Personal accounts in rubles and foreign currency were opened for each child affected by the military activities, and later the RDF asked public and private organizations, commercial structures, banks and ordinary citizens of the country to organize assistance to seriously injured children [16].

It is also very important that the standard of living of most Russian military doctors in those years was quite low: in the mid-1990s, 20 out of 35 employees of the Volgograd Hospital mentioned above did not have their own housing, their lack for new surgical equipment was acute [10]. In the midst of the second Chechen campaign, doctors from St. Petersburg also recognized the fact that they did not have expensive anti-shock suits or vacuum stretchers, which were common abroad [4]. At the same time, it should be noted that, despite the difficult socio-economic situation and permanent political instability in Russia of those years, the same Volgograd hospital as a whole was not deprived of attention and care of the authorities and community. He was assisted by the city and regional administrations, which allocated two cars and transport for the delivery of wounded soldiers from the plane to the hospital, as well as the local community. Many industrial enterprises in Volgograd supplied the medical institution with their own products, and ordinary citizens regularly visited wounded soldiers, brought them fruits or showed respect for them in other ways [10].

The results of the activities of Russian doctors in the North Caucasus at the turn of the XX–XXI centuries can be summed up using the following phrases about surgeons from St. Petersburg: ‘these people can disassemble and reassemble a person’ or ‘we are fighting for every centimeter of a limb’ [4]. These words are confirmed by official statistics, according to which the mortality rate in medical institutions steadily decreased during the largest military campaigns of the 20th century. Thus, it was 5.5%, 4%, 1.2% and 1% during the Great Patriotic War, the war in Afghanistan, and both Chechen campaigns, respectively [4]. As we can see, it was the fighting that became the most successful for our country in terms of saving human lives. It was Russian doctors who contributed to the restoration of the health care system of the rebellious republic and, in general, provided a high example of humanism and compassion for people. It was not by chance that the hospitals of various central ministries and departments were called ‘islands of mercy’. Largely because of their selfless work and courage, Russia managed to achieve a settlement of the Chechen crisis and, closer to the end of the second decade of the 21st century, establish calm, constitutional order and legality in the North Caucasus.

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