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

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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

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

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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

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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

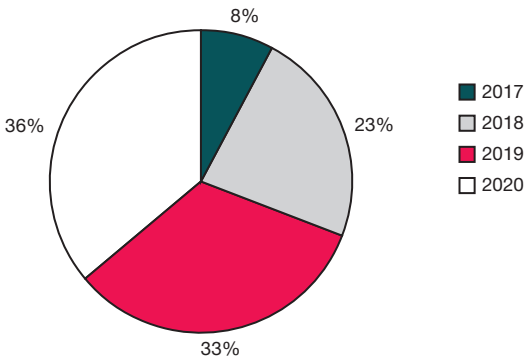

Figure 1. Distribution of Sponsor I's amendment output by year

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.

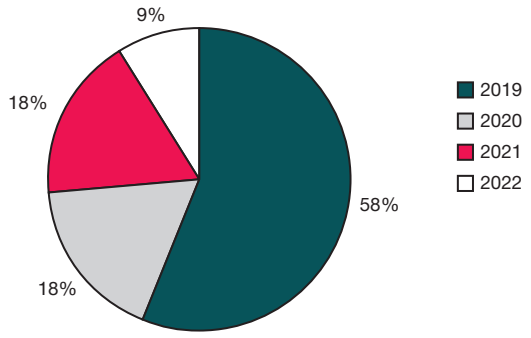

Figure 2. Distribution of Sponsor II's amendment output by years

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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