



Impact of COVID-19 on clinical trials protocol amendments

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Abstract

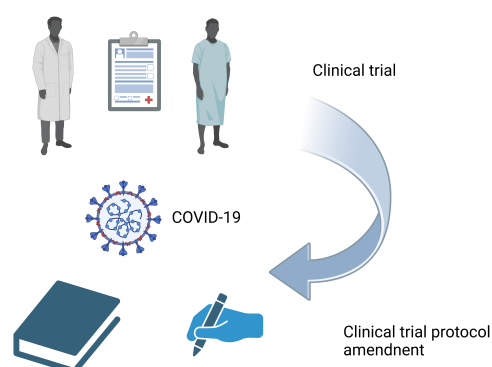
Introduction: The COVID-19 pandemic situation had a great impact on all spheres of people's lives. It also affected clinical trials as Sponsors, sites and investigators faced a number of problems, such as systematic IMP taking, adherence to protocol visits, efficacy evaluations, laboratory procedures, and analyses.

Materials and Methods: The amendments issued in 2020 were compared with the amendments issued in the previous three years 2017-2019. The literature about COVID-19 and its impact on clinical trials were analyzed. Clinical trial protocol amendments published in 2020 were studied to evaluate pandemic influence on ongoing clinical studies. Statistical processing of the results was carried out using the correlation analysis.

Results: The highest quantity of amendments was released in 2020 – 14 (36%). Fewer amendments came out in 2019 – 13 (33%), in 2018 – 9 (23%), and the fewest amendments were issued in 2017 – 3 (8%).

Conclusion: The existing system of clinical trial protocol creation is dependable and adequate. It allows reacting flexibly to unexpected challenges, like COVID-19, fully complying with the prescribed procedures and carefully observing participants' safety and well-being. That is why the current pandemic did not affect the number of protocol amendments.

Graphical abstract:



Keywords

COVID-19, clinical trials, pandemic 2020, protocol amendments

Introduction

No doubts that society, trade, economy and environment are being influenced nowadays by virus SARS-CoV-2 pandemic; especially the health care system all over the world is under the most load now. These circumstances definitely affect the process of handling clinical trials of new drugs. The existing situation makes it more difficult (Kunz et al. 2020) as Sponsors, sites and investigators are facing a number of problems.

To begin with, these problems are connected primarily with possible risks of virus spreading among clinical trial participants, other patients and medical staff (Asaad et al. 2020). Several trials were put on hold or patients' enrollment was slowed down (Ledford 2020; Upadhaya et al. 2020) due to government restrictions on travelling and border closures, which caused the threat of unavailability of IMP and necessary equipment due to supply disruptions. Another reason for delayed trials were participants' quarantine or sites closure because of its reclassification for activities against COVID-19 (Akacha et al. 2020; Vissers et al. 2021).

The impact of the above-listed difficulties on ongoing clinical trials is fatal as health care systems and society altogether were not ready to cope with this situation.

In this connection, Sponsors need to take into account all local regulations and imposed restrictive measures, as well as to respond faster than usually to a rapidly changing reality.

Pandemic affects the world's health care authorities' focus and approach to document's review. That was

reflected in the fact that the authorization process of new clinical trials was slowed down and even more terminated, for example, the first draft of the EU Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic recommended that the initiation of new trials be assessed critically unless these trials are aimed to test new treatments for COVID-19 (Hasford 2020).

Russian Health Care Authorities also had to react to the changes. According to the data, in 2020 (AOKI 2021) the time scale of obtaining an approval of amendments in clinical trial protocols increased from 48 to 65 days, the time period for obtaining approvals for new clinical trials increased from 87 to 103 days and the time periods for obtaining an import IMP license and import/export biological samples approvals increased from 15 to 17 days and from 20 to 22 days, respectively, when compared with 2019.

All the above-mentioned problems may impede proper flow of procedure sequence prescribed by the protocols: systematic IMP taking, adherence to protocol visits, efficacy evaluations, laboratory procedures and analyses, adequate monitoring by Sponsors, which, in turn, may affect the validity and interpretation of the research data (Meyer et al. 2020; Sathian et al. 2020).

On the one hand, ensuring the safety of the trial participants is the priority task for Sponsors (Beane et al. 2020; Singh and Pankaj 2020), but, on the other hand, another important issues are to use the possibility of obtaining validity of the data and to comply with all the procedures prescribed by the protocol. In this connection, pharmaceuticals companies were forced to solve the issue of continued use of IMP for enrolled participants and to change monitoring methods for the ongoing studies.

As usual, all these changes connected with safety and patients' well-being, clear instructions for investigators for each trial must be also registered by publishing clinical trial protocol amendments. An additional purpose of these amendments is to be ensured against financial losses in case of expensive trials closure (Moore et al. 2018).

For all those protocol amendments, publishing is a routine process, which is connected with the new standards of care; changes related to medications that were approved for use before or during the clinical trial; renewal of safety data; requests from regulators and other supervisory organizations. Moreover, the reason of these protocol amendments can be changes in the inclusion criteria due to changing the research strategy or problems with recruiting patients (Chow and Jun 2005; Getz et al. 2011).

In an ideal scenario, a clinical trial protocol must be detailed and comprehensive, as well as predetermined in perspective, as anything that is done *ex post* can affect the validity of the data obtained during the trials; however, a direct link was found between protocol complexity and frequency of publishing protocol amendments in a 2008 study by the Tufts Center (Getz et al. 2008).

In practice, it is impossible to prevent everything that leads to the release of amendments, and, accordingly, to an increase in the research cost.

Thus, the problem of determining and minimizing the risks of the release of clinical trial protocol amendments remains open.

Materials and Methods

The current analysis includes literature sources to evaluate possible impact of COVID-19 pandemic on different aspects of ongoing clinical trials in general. The real-life example of Sponsor's clinical studies crossing through pandemic 2020 is introduced by evaluation of causes of 39 protocol amendments that were made to 20 protocols approved by the Russian health care authorities over 3 years from 2017 to 2019.

Statistical processing of the results was carried out using the correlation analysis.

Results

The highest quantity of amendments was released in 2020 – 14 (36%). Fewer amendments came out in 2019 – 13 (33%), in 2018 – 9 (23%) and the fewest amendments were issued in 2017 – 3 (8%).

Two out of the three amendments, which were released in 2017, were issued due to health authorities' requests, and the last one was connected with the updated clinical trials' information.

In 2018, nine amendments were released. The first changed protocol was connected with statistical section updates, the next two – with health authorities' requests, another four amendments were related to general corrections of protocols and in the last two amendments, minimal residual disease points were added.

Thirteen amendments were published in 2019. Four of them were initiated by health authorities and connected with clarifying the risks and efficacy of the IMP and concomitant therapy. Each of the below mentioned amendments was released due to several reasons: increased the number of countries participating in trials; describing and improving trial procedures; updating the statistical section; adding another dosing regimen and correcting lexical errors.

It was found out that the quantity of amendments reached its maximum in 2020 (14) compared with the previous years: 5 of the 14 corrected protocols (38%) are related as usual to health authorities' requests (Fig. 1) and only one amendment (8%) was caused by continued COVID-19 pandemic situation because of difficulties in arranging site visits by patients, and, accordingly, in obtaining a drug. In this connection, the schedule of visits was corrected and the possibility of delivering IMP to patients at their homes was provided. Each of the following amendments accounts for 8% of the total amendment number in 2020. They were issued as a regular process of conducting clinical trials. They were connected with dosage changing, with the identified risk of chronic illnesses reactivation during treatment, with the adding recommended concomitant therapy for participants, additional patient allocation parameters and general information about the study, the latter two relating to a change in procedures (15%).

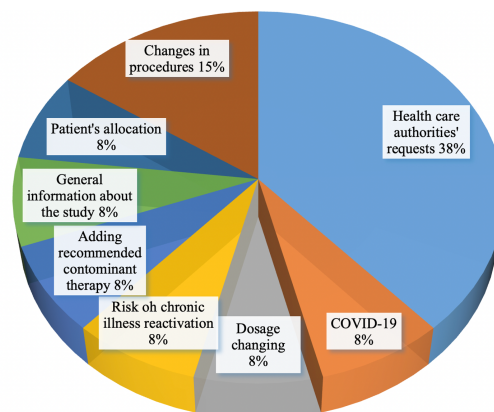


Figure 1. Reasons for the clinical trial amendments release in the year of the largest number of amendments of all analyzed years – in 2020.

Thus, the distribution pattern is repetitive, with the exception of a large number of amendments related to requests from regulators and changes in prescribed procedures. The amendment caused by COVID-19 situation accounts for only 8% of all the amendments and does not stand out among the obtained quantitative and percentage distribution.

Within four years, the quantity of amendments increased along with the quantity of trials in progress (Table 1). Comparing a number of current protocols and number of amendments issued to them, a direct connection was found (correlation coefficient = 1). Also, determining the dependence of the number of current protocols and the number of corrections for one current

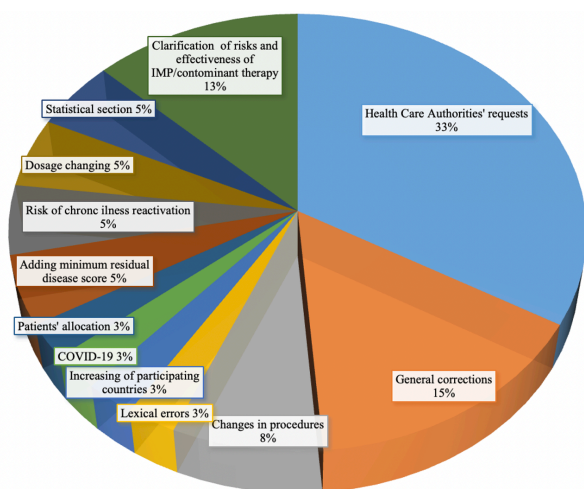
Table 1. Distribution data of number of protocols amendments

Year	Quantity of ongoing trials	Quantity of amendments released	Quantity of amendments per 1 ongoing trial	Quantity of amendments from health care authorities	Quantity of amendments from health care authorities per 1 clinical trial
2017	5	3	0.6	2	0.67
2018	11	9	0.8	2	0.22
2019	15	13	0.9	4	0.30
2020	13	14	1	5	0.35

study, a direct interconnection was found, namely, the correlation coefficient is 0.9, which indicates a direct dependence. Thus, 2020 was no exception to this dependence: the analyzed data showed the maximum number of amendments for the number of current protocols, since 14 amendments were issued for 13 current studies, that is, 1 amendment per 1 current protocol.

At the same time, on average, one protocol accounts for 0.4 amendments due to requests from regulatory authorities.

Let us consider the distribution of the reasons for the release of amendments for all the listed years (Fig. 2).

**Figure 2.** Distribution of reasons for the release of clinical trial protocol amendments for all analyzed years (2017-2020).

Discussion

Based on the data obtained, we can say that the number of amendments in 2020 reached its maximum among all the years analyzed. The 13 analyzed amendments are related to routine changes during the study associated with the identification of serious adverse events and the refinement of IMP dosage, changes in procedures and analyses for patients, and with statistical aspects. All the above mentioned amendments were issued on a regular basis in the previous 3 years as well as in 2020.

However, only one amendment for the last year analyzed was released in response to the ongoing COVID-19 pandemic

Obviously, this amendment brought about certain physical and material inconveniences to the pharmaceutical company due to postponement of visits and organization of drug delivery events, and also affected the research team, making them do additional paperwork. However, if we consider this amendment as a percentage to the other revised amendments, it accounts for only 3% of all and it does not fundamentally change the picture of distributing the reasons of clinical trial protocol amendments.

This COVID-19 amendment was released due to a Sponsor initiative, which demonstrates a high level of concern for patient safety, and therefore there was no need for regulatory intervention.

Conclusion

To sum up, based on the distribution obtained and only one issued amendment in response to the pandemic situation due to difficulties in arranging site visits by patients, and accordingly, in obtaining a drug, due to which the schedule of visits was corrected and the possibility of delivering IMP to patients at their homes was provided, we can conclude that the existing system of creating clinical trial protocols is dependable and adequate. Moreover, it allows reacting flexibly to unexpected challenges, like COVID-19, fully complying with the prescribed procedures and carefully observing participants' safety and well-being. That is why current pandemic did not affect the number of protocol amendments. As a result, Sponsor can get reliable data at the end of the ongoing research.

Conflicts of Interests

The authors have declared that no competing interests exist.

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