The impact of the COVID-19 pandemic on the risk of clinical trial protocols amendments

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Annotation. Obviously ongoing COVID-19 pandemic situation had a great impact on all people's lives and spheres all around the world. Clinical trials aren't the exception. The goal was to evaluate the pandemic influence on probability of protocol amendments emergence. Our analysis indicated that the existing system of clinical trials protocols creation is proved to be quite adequate and an unforeseen circumstance as a pandemic have had little effect on the number of amendments.

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

Introduction

Obviously ongoing COVID-19 pandemic situation had a great impact on all life spheres: economics, society and, of course, on health care, including clinical trials. Many of them, especially clinical trials of innovative drugs, are international. Global lockdown measures, air, sea and overland transportation restrictions, and implemented in other counties limitations and rules all around the world caused by pandemic, created critical problems to conducting global trials. Clinical research is an important part of scientific research in medicine. All local instructions and COVID-19 implemented limitations are needed to take into consideration by Sponsor as the current situation makes it difficult to conduct clinical research around the world [1].

Despite of ample resources turned on COVID-19 preventive and treatment trials, other treatment methods and disease prevention clinical trials not connected with COVID-19 are still ongoing.

Clinical trial Sponsors and participants are faced a number of problems due to pandemic situation. Firstly, some risks of viral spread among study participants, investigators and medical workers may arise. [2]. Secondly, there might be a problem with clinical trials conducting due to possible quarantine of study participants, hospital staff or their isolation caused by government travel ban. Thirdly, it is conceivable that clinical trial sites will be closed or there will be investigator medical product supply problems. Furthermore, there is a chance of overload and turned of healthcare system on COVID-19 disease control measures [3,4]. All these problems may have a great impact on data consistency and its interpretation obtained as a part of the studies, while the quality of clinical trials must stay high despite of the changes in the world around [1].

Before each clinical trial start-up a clinical protocol is created and approved to describe how and why it should be conducted [5]. Considering the fact that clinical trials are expensive and long-continued most of ongoing trials were planned before the beginning of pandemic [6,7] . Consequently, these pandemic risks weren't taken in consideration in these protocols.

As new facts which can effect on clinical trials results can appear during its conducting GCP provides the possibility of protocol updates [8]. These amendments can make trails more complicated and expensive [9].

Goals

To evaluate the pandemic influence on probability of protocol amendments emergence, we drew a comparison between amendments to ongoing non-COVID-19 trials, which were published in 2020, and amendments published in previous years.

Materials and methods

For possibility creating of protocol amendments evaluation, we drew a comparison between amendments to ongoing trials, which were published in 2020 and amendments published in previous years. We carried out an analysis of amendments (2017-2020 years) for Sponsor's protocols which were approved by Russian Health Care Authorities between 2017 and 2019 years included. All these trials didn't relate to any drugs against COVID-19.

Results and discussion

Facing a great number of amendments during these 4 years the majority of them had objective reasons to be published: ongoing drugs observations, legislations amendments etc. The quantity of protocol amendments within 4 years had increased. The minimum quantity of them was shown in 2017 -3 (8%) in 2018 - 9 (23%), little more in 2019 - 13 (33%). The biggest quantity was in 2020- 14 (36%).

In 2017 3 amendments were published, 2 of them were initiated by health authorities request and the last one was related to trail information update.

In 2018 9 amendments were announced and only 2 of them were connected with health authorities, 4 amendments were related to general corrections, 2 amendments were connected with adding minimal residual disease points and the last one with statistical section updates.

In 2019 from 13 published amendments 4 of them were initiated by health authorities, 4 were connected with clarifying the risks and efficacy of the investigational drug and concomitant therapy, one-with statistical section updates, one more was announced due to multiplication of participated in trials countries, another one to describe and improve trial procedures and one-by-one amendments connected with lexical errors and with adding another dosing regimen.

Despite of in 2020 the quantity of amendments reached its maximum (14) basically they were not related to COVID-19 pandemic situation. Thus, one amendment was associated with the identified risk of hepatitis B reactivation during treatment, the other with the addition of drugs as recommended concomitant therapy for patients participating in the study. One was due to a dosage change, additional patient allocation parameters and general information about the study, and the other two related to a change in procedures (15%). Large percentage (38%) of amendments was connected with health authorities' requests.

Based on the data obtained, we can say that the quantity of protocol amendments was maximum in 2020 and the entire quantity of protocols were increased as the direct dependence was shown, the scaling factor r=1. Proportion of amendments initiated by health authorities haven't been

changing within 4 years, this means that health authorities didn't implicate in isolated trials it only published some recommendations. Meanwhile their requirements to conducting clinical trials haven't been changed and they are still controlling all ongoing studies.

In 2020 only one amendment (8%) was related to COVID-19 pandemic situation and was published due to difficulty of performing visits by patients and getting Investigational Medicinal Product. In this connection, schedule of visits was corrected and an opportunity of home investigational medicinal product delivery was afforded. This amendment brought certain physical and material inconveniences to the pharmaceutical company due to the organization of drug delivery events and the postponement of visits, and also affected the research team due to additional paperwork. At the same time, distribution pattern of the reasons creating protocol amendments has not been changed dramatically.

Thus, we can conclude that the existing system of clinical trials protocols creation is proved to be quite adequate. Even such an unforeseen circumstance as a pandemic have had little effect on the structure of the protocols and the number of amendments. As a result, despite the pandemic situation in the world, the Sponsor can get reliable data at the end of the ongoing research.

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