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Impact of COVID-19 on Pharmaceutical Industry: Status of Clinical Trials and Mitigation Strategies

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Resumen

Background: COVID-19 could affect clinical trials because avoidance of close contact between people constitutes one of the approaches that have been recommended to ensure that individuals do not become exposed to the coronavirus.

Objectives: To discuss the impact of COVID-19 on clinical trials within the pharmaceutical industry. In addition, the paper examines some strategies that can be adopted to cope with impact of COVID-19 on clinical trials and thus ability to continue conducting the trials.

Methods: This is a narrative review article. We provided a synthesis of current literature and guidelines obtained from searches on many electronic databases (PubMed/Medline, EMBASE, and Cochrane Library), Google search engine, the United States (US) Food and Drug Administration (FDA) website, and hand searches on the bibliography of the articles.

Results: There is a significant impact of COVID-19 on clinical trials. The impact includes: undermining sponsors' economic ability to fund clinical trials, social distancing, impeding recruitment of participants for non-COVID-19 clinical trials, discouraging participants from visiting clinical sites due to fear of COVID-19 infections, and making trial staff to opt for remote working. The US FDA published new guidelines to be applied during the ongoing pandemic. Mitigation strategies to ensure continuity of clinical trials include: adopting participant enabling measures, modifying clinical trial protocol, providing logistical and supply chain management support, embracing remote data review and clinical site monitoring, and offering extra site support services.

Conclusions: COVID-19 pandemic is disrupting the initiation and continuing ongoing clinical trials. Guidelines have to be followed and strategies for mitigating adverse impacts of COVID-19 need to be applied. Modifying monitoring methods should be done to accommodate the constraints posed by the ongoing COVID-19 pandemic.

Keywords: Coronavirus; COVID; SARS; Clinical trial; Guidance; Guideline; Recommendation; Mitigation.

Introduction

Coronavirus Disease of 2019 (COVID-19) refers to an infectious respiratory ailment brought about by a strain of coronavirus first discovered in December 2019. Having originated from Wuhan, China, the disease has spread to virtually every country across the world, thus becoming a global pandemic. Symptoms of COVID-19 include fever, dry cough, and headache. COVID-19 patients exhibit respiratory symptoms and there are many deaths due to this disease. Individuals with existing health problems and older persons have a high likelihood of developing severe illness. The COVID-19 pathogen spreads mainly through direct contact with nose discharges or saliva droplets expelled when a patient sneezes or coughs.

Currently, there are no definite treatments or vaccines for COVID-19. Recommended measures for slowing down transmission and protecting oneself from being infected with COVID-19 include: washing hands frequently with soap, using alcohol-based sanitizers to cleanse hands, wearing face coverings such as masks, and avoiding touching face with unwashed hands [1]. COVID-19 could affect clinical trials because avoidance of

close contact between people constitutes one of the approaches that have been recommended to ensure that individuals do not become exposed to the coronavirus. Among other recommendations, this tactic encourages a person to always ensure there is physical distance of at least 2 meters between him/herself and other individuals whenever he/she is outside his/her home. The approach also discourages people from gathering in groups and attending mass congregations where there is a likelihood of overcrowding.

Considering that one motivation behind this approach is the realization that certain individuals could spread the coronavirus despite not exhibiting symptoms, the tactic is likely to cause people to shrink back from the prospect of participating in clinical trials [2].

Within this context, the objective of the paper is to look at the impact of COVID-19 on the pharmaceutical industry. Specifically, the paper focuses on how COVID-19 has affected clinical trials within the pharmaceutical industry. In addition, the paper examines some strategies that can be adopted to cope with impact of COVID-19 on clinical trials and ability to continue conducting the trials.

Methods

This is a narrative review article. We aimed to discuss the impact of COVID-19 on pharmaceutical clinical trials and identify current recommendations and/or guideline that describe and provide detailed context into mitigation strategy to be able to initiate or continue clinical trials during COVID-19 pandemic. We provided a synthesis of current literature and guidelines obtained from searches on many electronic databases (PubMed/Medline, EMBASE, and Cochrane Library), Google search engine, the United States (US) Food and Drug Administration (FDA) website, and hand searches on the bibliography of the articles. The main keywords used to aid the search were: coronavirus, COVID, COVID-19, SARS-2, Severe Acute Respiratory Syndrome, SARS-CoV-2, clinical trial, guidance, guideline, and recommendation.

Results and Discussion

Impacts of COVID-19 on Clinical Trials

General Impacts: Multiple economic indicators highlight that COVID-19 is negatively impacting the global economy on a massive scale. Numerus international trade and economic activities are experiencing the adverse effects of the pandemic. For instance, in many countries, international passenger travel has been suspended. Accordingly, global GDP and trade volumes are projected to drop sharply in the first 6 months of 2020. To support this forecast, the US Department of Commerce has reported that the US GDP decreased by 4.8% within the first three months of 2020. Equally, citing the measures currently being taken to contain COVID-19, the Organization for Economic Cooperation and Development (OECD) has forecasted that global GDP may contract by 2.0% in every month throughout 2020. Cumulatively, this reduction of GDP will amount to 24% by the end of December 20202 [3]. Because of such harmful effects on the world economy, COVID-19 is bound to adversely impact the economic circumstances of organizations and firms that usually finance clinical trials. Owing to such reduced financial capability, these sponsors (include pharmaceutical companies) may be forced to reduce the amount of money set aside to be spend for clinical trials. COVID-19 has also brought about difficulties in the recruitment of participants for clinical trials not related to this disease. These include trials focusing on rare diseases. This difficulty is partly deriving from the fact that, in multiple countries, COVID-19 containment measures such as lockdowns are preventing participants from accessing clinical sites [4]. Such problem is exacerbated by the fact that it is no longer possible for researchers to employ the conventional tactic of increasing the number of clinical sites to boost the speed of recruitment. The highly infectious nature of COVID-19 cannot not allow use of such strategy. Further, COVID-19 is undermining clinical trials because participants are unwilling to visit clinical sites because of fear of being infected with coronavirus.

Additionally, in cases where a clinical site is a healthcare institution such as a hospital, priority is being given to the need to treat COVID-19 patients [4]. This situation is undermining the continuity of both ongoing and planned clinical trials. In supporting this assertion, the European Medicines Agency warns that COVID-19 pandemic is projected to disrupt the carrying out of multiple ongoing trials by impeding the gathering, scrutiny, and construing of data deriving from clinical trials [5]. According to Upadhaya et al. (2020), 86% of the surveyed investigators leading oncology clinical trials in Europe had lower rate of patients' enrollment after COVID-19 [6]. Table 1 shows an overview of the impacts of COVID-19 on the rate of patients' enrollment into oncology clinical trials in Europe, US, and Asia.

Equally, because of COVID-19, certain individuals responsible for running clinical trials are demonstrating apprehension about performing such work due to the fear of being infected by coronavirus. These individuals are thus exhibiting an inclination to work remotely [4]. Nevertheless, considering that the running of clinical trials typically requires a person to be present at a clinical site, such attitudes are prejudicing clinical trials. Similarly, COVID-19 is prompting some entities responsible for running clinical trials to halt recruitment in ongoing studies and postpone planned studies so as to engage in other activities such as conducting testing for COVID-19 [7].

COVID-19 is further affecting clinical trials based on the fact that, if a participant becomes infected with this virus, the outcomes of a study would be affected. For instance, if a clinical trial is related to cardiology and a trial participant is infected with COVID-19, the coronavirus would negatively affect the results of the trial. Equally, if a participant in a clinical trial (that is not related to COVID-19 but focusing on the respiratory system) becomes infected with the coronavirus, the results would be damaged. This is because COVID-19 primarily affects the respiratory system, particularly the lungs [8,9]. In addition, participants in a clinical trial may come into contact with a COVID-19 patient or someone suspected of having the disease, thereby being required to practice self-isolation. Such happening would make it difficult for the individuals running a trial to sustain their medical

Table 1: Enrolling Patients in Ongoing Oncology Clinical Trials (after COVID-19)*.

Region (# of surveyed investigators)	Rate of Patients' Enrollment		
	No Enrollment	Lower	Same
Europe (n=7)	0%	86%	14%
US (n=10)	20%	60%	20%
Asia (n=5)	20%	20%	60%
*Information derived from Upadhaya et al. (2020).6			

supervision of the participants. Consequently, the execution of trials would be negatively impacted by, for instance, being terminated prematurely. Accordingly, participants would not be able to complete the scheduled trial visits and would thus not be provided with the necessary investigational medicinal products (IMPs) [4]. **Regulatory Impacts:** COVID-19 has specifically affected clinical trials in that, in March 2020, the US FDA published new guidelines to be applied during the ongoing pandemic. These rules are based on three principal considerations: (1) prioritizing the safety of participants in clinical trials, (2) ensuring conformity to excellent clinical procedures, and (3) reducing risks to the integrity of clinical trials. The guidelines explain the procedures that should be adhered to with regard to: ongoing clinical trials with procedures that have been already prepared, and clinical trials with procedures or policies that are yet to be developed. In cases where procedures have been already prepared for ongoing clinical trials, the FDA guidelines outline four sets of requirements. Firstly, if immediate modifications to informed consent procedures or study protocol are needed, administrators of clinical trials should alert the relevant institutional review board(s) or independent ethics committee(s) (IECs). Administrators of clinical trials also need to consult the FDA's appraisal departments regarding potential substitute plans for administering study products within conventional health care settings. In addition, administrators of clinical trials should assess substitute methods for evaluating safety such as through use of virtual technology. Administrators of clinical trials further need to enhance utilization of remote/central programs in maintaining supervision of clinical sites where on-site surveillance is not possible. According to a survey (based on 198 responses) published by Upadhaya et al. (2020), 50%-82% of the responses shows the awareness of current or future implementation of strategies being considered for clinical trial assessments to mitigate COVID-19 pandemic (Table 2) [6]. On the other hand, where procedures/policies for clinical trials are yet to be developed, the FDA rules require managers of clinical trials to develop, apply, and/or amend procedures/policies to control the conduct of studies and safeguard participants [10].

Furthermore, the aforementioned FDA guidelines mandate administrators of clinical trials to record the impacts of COVID-19. Such documentation needs to describe the conduct of studies in the context of interruptions deriving from COVID-19. Records should also analyze the effectiveness, effects, and safety of whatever emergency measures implemented. The documentation also needs to describe the effected sites and participants, including providing an account of how participation has been changed [10].

Strategies for mitigating adverse impacts of Covid-19

Ensuring continuity of clinical trials

To ensure the continuity of clinical trials during the COVID-19 pandemic, the following mitigation strategies could be implemented: adopting participant enabling measures, modifying clinical trial protocol, providing logistical and supply chain management support, embracing remote data review and clinical site monitoring, and offering extra site support services. The strategy of adopting participant enabling measures entails implementing any necessary measures to guarantee that clinical trial participants have the capacity to perform required trial activities remotely. A viable approach to implementing this proposal is use of blockchain-based system that would enable participants to perform various activities such as the provision of written informed consent in an uncomplicated and secure manner [11]. Alternatively, this strategy involves taking steps to guarantee that, upon reaching a trial site, participants obtain the support necessary to help them carry out the needed trial activities. Such support would help to minimize the risks incurred by participants and increase the benefits they derive from participating in clinical trials [12].

The mitigation strategy of modifying clinical trial protocol entails consideration and application of substitute trial implementation models. Such measure nevertheless requires the managers of a clinical trial to obtain the requisite support from the relevant regulatory authorities [13]. Equally, the strategy of providing logistical and supply chain management support involves offering any necessary assistance to guarantee the remote management of drug supply systems and laboratories. A useful approach to such remote management is the deployment of a data warehouse that integrates participant data and makes it available to members of research crews in a timely fashion [14]. Similarly, the strategy of embracing remote data review and clinical site monitoring entails implementing adjustments to ensure that data is monitored remotely. This is in a bid to resolve the COVID-19-based problems of reduced clinical site personnel and impaired mobility of clinical research associates (CRAs). One technique of facilitating remote data review is through use of implantable electronic devices on participants [15]. The mitigation strategy of offering extra site support services involves providing assistance in form of extra training for staff and additional personnel [16]. Such initiatives would reinforce a site and thus boost its capacity to attain its objectives successfully.

Table 2: Strategies Being Considered for Clinical Trial Assessments to Mitigate COVID-19*.

Strategies or Technologies	Percentage of the responses shows the awareness of current or future implementation*
Telehealth	82%
Alternative Location of Assessment	73%
Reduced Site Visit	73%
Remote Electronic Medical Records	73%
Shipping Oral Drugs	64%
Virtual Site Visits	59%
*Information derived from a survey (based on 198 responses) published by Upadhaya et al. (2020).6	

Modifying monitoring methods

While ensuring conformity to relevant regulatory rules and maintaining open communication with stakeholders such as participants and contract research organizations (CROs), [17] managers of clinical trials may modify monitoring methods to accommodate the constraints posed by the ongoing COVID-19 pandemic. Such modifications would prioritize the need to ensure the integrity of data [18] and ensure the safety of participants [19]. These modifications can be implemented in the following areas: risk assessment, adoption of virtual working regimes, and use of analytics to guide clinical trials.

The area of risk assessment would entail tracking the condition of sites to ensure they are conducive to clinical trials. Such tracking would enable managers of sites to identify needs that are specific to particular sites. Site managers would thereby allocate hazard levels for participant populations [20]. Managers would also consider and determine the appropriate geographical location of the CRAs in a clinical trial. Any existing restrictions to movement and their impact on trials would also be analyzed. The topic of managing IMPs and ensuring their accessibility to participants is also examined [21].

The area of adoption of virtual working regimes would involve building on existing risk-based supervisory experience. Clinical study teams would thus adopt the policy of visiting sites remotely by contacting individuals at sites through telephone [22]. Additionally, whenever possible, trial teams would adopt policies of verifying sources of data and reviewing such data remotely [23]. Furthermore, trial teams would train both themselves and participants concerning the needs and requirements associated with remotely visiting sites. The area of using analytics to guide clinical trials entails deployment of cutting-edge analytics technologies to identify the neediest sites. Analytics tools would also facilitate remote supervision of participant and site risks and determination of priorities for making on-site visits. Furthermore, analytics would facilitate execution of periodic data integrity evaluations and investigations concerning participant safety indicators. Using analytics, it is also possible to appraise clinical trial protocols for non-conformity to established guidelines [24]. Additionally, analytics can help in installing site risk evaluation tools, thus guaranteeing continuous assessment.

Advantages of addressing changes in clinical trial due to Covid-19

The critical advantages of addressing changes in clinical trials due to COVID-19 include having a momentum for change and a call for collaboration among multiple stakeholders (i.e., academic researchers, pharmaceutical companies, professional organizations, regulators, and patients). For example, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research released recommendations focusing on the continuing effort to broaden eligibility criteria to make oncology clinical trials more representative and inclusive [25,26]. According to Connie Szczepanek, RN, BSN, CCRP, of Cancer Research Consortium of West Michigan, many changes have been performed in oncology clinical trials due to COVID-19 pandemic and these changes should be adopted permanently [26]. Another example is the ongoing efforts by the US FDA, the Advisory Committee of Clinical Trials and Transformational Research, and ASCO to improve clinical research post-COVID-19. In addition, many clinical investigators, academic researchers, pharmaceutical companies, and professional organizations shared or published the lessons they learned from COVID-19 and provided their insights to continue working on clinical trial post-COVID-19 pandemic [25-27].

Study Limitations

This study used a narrative review methodology to: (1) collect information related to the impact of COVID-19 on clinical trials (within the pharmaceutical industry), and (2) identify strategies that can be adopted to cope with impact of COVID-19 on clinical trials. Although one of the traditional methods of reviewing the literature has been the narrative review, several limitations are associated with a narrative review methodology. First, there is no rule on how to obtain primary data and how to integrate the results; that is the subjective criterion of the reviewers. However, our search was conducted using specific keyword on many electronic databases to identify related information within the scope of this review. Second, the reviewers did not conduct a quantitative research to synthesize the data found in the different publications. Therefore, selective bias may be involved while selecting the articles to be included in this narrative review. However, the reviewers did not exclude articles unless if they are not related to the scope of this study.

Conclusions

COVID-19 pandemic is disrupting the initiation and continuing ongoing clinical trials. Guidelines have to be followed with regard to: ongoing clinical trials with procedures that have been already prepared, and clinical trials with procedures or policies that are yet to be developed. Strategies for mitigating adverse impacts of COVID-19 need to be applied. Modifying monitoring methods

should be done to accommodate the constraints posed by the ongoing COVID-19 pandemic.

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