Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Conducting Clinical Research in the Era of Covid-19

The emergence of Corona Virus Disease 2019 (COVID-19) caused by the novel SARS-CoV-2 virus in Wuhan, China in December 2019, raised many challenges to clinical research. Even now, investigators, industry sponsors, and institutional review boards/ethical committees (IRB/EC) struggle to maintain the safety of trial participants and researchers, while promoting the continuity of ongoing clinical studies. COVID-19 has spread to more than 215 countries, infected more than 8 million people, and caused close to 500,000 deaths globally as of this submission.[1] The United States is caring for the largest number of cases, currently at 2 million, with over 25,000 deaths.[2] Without a proven vaccine or treatment, the mortality rate in the United States is projected to be as high as 135,000-140,000 by August 2020. By comparison, the H1N1 influenza pandemic of 2009 infected 60.8 million individuals and resulted in 12,469 deaths in over 12 months in the United States (Centers for Disease Control and Prevention, CDC, estimation).[3] In general, it is estimated that a person infected with COVID-19 can infect 3 others while an individual with the H1N1 influenza virus infected 1.4-1.6 and those with the seasonal influenza infected about 2.[4,5] Clearly, the transmission and mortality rates are what makes COVID-19 a global concern and a source of disquietude.

The conduct of clinical studies changed soon after the U.S. Department of Health & Human Services (HHS) issued a COVID-19 Public Health Emergency on January 31, 2020.[6] The FDA, investigators, industry sponsors, and IRBs/ECs, among others, were required to act quickly to assess the status of ongoing studies and restructure research processes accordingly. Unanticipated deviations to protocols became unavoidable, as subjects were unable to attend study visits due to travel restrictions, clinic closures, and quarantine requirements. Elective surgeries and protocol-specified procedures were postponed to diminish environmental contamination and to preserve limited personal protective equipment (PPE). Research staff were instructed to work remotely and study enrollment was only allowed for trials required for a participant's health (e.g., oncology treatment protocol). Other challenges included possible interruptions in the supply of investigational product and other clinical trial shipments. The "stay-at-home orders" issued by various governmental authorities appropriately emphasized the safety of subjects, but negatively impacted recruitment and enrollment into clinical studies and affected data collection.[7]

The pandemic has also stimulated new clinical research as investigators desperately search for ways to learn about the virus and its impact, characterize the patient populations affected, and test the efficacy of candidate interventions. In the United States alone, there are 17,500 clinical trials reporting a status of currently recruiting new subjects that are possibly affected by the COVID-19 pandemic. Additionally, the Food and Drug Administration (FDA) accelerated their processes for evaluating requests for investigational new drug (IND) applications with the creation of the Coronavirus Treatment Acceleration Program (CTAP).[8] Oversight organizations altered their standard operating procedures and provided guidance to reduce the regulatory burden imposed by the pandemic on investigators. The FDA also issued a guidance document in March 2020 (updated April 16, 2020)[9] to assist stakeholders in clinical research with the purpose of acknowledging protocol deviations and to provide recommendations to protect the safety of subjects and maintain the integrity of the clinical trials (Table 1).

Healthcare facilities and clinical trial sites quickly revised old and developed new policies and procedures to provide continuity of care to their personnel, patients, and communities. Most clinical research sites have adopted these practices in conjunction with guidance from industry sponsors and local or centralized IRB/ECs. The FDA guidance document also emphasized the need for stakeholders to develop emergency policies and procedures to maintain the conduct of clinical studies (informed consent, study visits, procedures, safety monitoring, trial drug accountability, changes in research staff, and study monitoring processes) and protect study participants in ways that are in accordance with local, regional, and national regulations. The table summarizes selected recommendations for conducting clinical research during the era of COVID-19.

POST COVID-19 CLINICAL RESEARCH

As clinical sites and other healthcare facilities begin to re-open, they are faced with more challenges on how to do this safely. Clinical research visits follow the same procedures designated by the local healthcare facility. Assessment tools are being developed to determine levels of risk and triage patients. Patients are being prescreened for a number of symptoms associated with infection by COVID-19, and if they have been in contact with another individual who either tested positive for or had COVID-19. It is generally recommended that patients entering clinical areas wear masks and have their temperature taken. Physical distancing should be practiced in patient registration areas as well as waiting rooms. Taking patients directly to an exam room is best. Hand hygiene by both patients and staff should be done prior to entering the room and upon leaving. Appropriate PPE designated by the patient risk assessment should be worn by the staff at all times and during disinfection of the exam room. The exam room is then left empty for a period determined by the amount of air exchange or ventilation present in the exam room. As we are learning

TABLE 1. Overview of the FDA guidance for conducting clinical research during COVID-19 pandemic.[9]

Oversight
• Investigators should determine if it is in the best interest of the subject to continue in a trial and/or continue the use of a trial drug. • In accordance with research informed consent requirements, the subject should be informed of any protocol changes that could affect their participation, as this is new relevant information. • Industry sponsors should be in contact with each investigative site to provide guidance on safety procedures to be continued such as labs or other vital status measurements. • IRBs/ECs may need to change their review processes if they are accustomed to meeting in person or submissions are still on paper. Some central IRBs/ECs already have electronic submissions in place and committee members meet via a secure teleconference format.
Study visits:
• Alternative means of obtaining data may need to be incorporated after approval from the FDA or IRB/EC. For example, telehealth visits (telephone calls and video conferencing) can be substituted for in-person visits.
Study drug, supplies and equipment:
• A process for the safe shipment of the investigational product or trial drug directly to the subject that meets sponsor approval as well as local, state, and federal laws can be developed. • Similarly, contingency measures to maintain the manufacture and supply of study drug to research sites during a pandemic or other emergency should be implemented.
Procedures
• Some protocol-specified assessments for efficacy will most likely be delayed or missed and could affect the integrity of the study. However, protocol specified procedures that put the subject or research staff at risk for contracting the virus should be postponed to a later date. These include situations that require close respiratory/facial contact and/or aerosol generating procedures (e.g., pulmonary function testing, nebulization, bronchoscopy, collection of sputum samples, intubation). • Sponsors should seek guidance from the FDA when such protocol changes are considered to affect proposed study endpoints and/or statistical analysis.
Communication:
• In accordance with research informed consent requirements, investigators should maintain contact with trial subjects and keep them informed of protocol changes that could affect their participation (new information). • Sponsors should be in contact with each investigative site to provide guidance on safety procedures to be continued such as labs or other vital status measurements.
Data integrity
• Sponsors and investigators are required to document and maintain a log of all missing data and protocol deviations in the study regulatory files. • Any deviations and changes to the protocol should be reported to the local or centralized IRB/EC as soon as possible. As it relates to COVID-19, the documentation should include a description of the deviation/missing data, its relationship to COVID-19, subject ID (if applicable), and any mitigation instituted. • IRB/ECs should acknowledge and render a decision as to whether it is safe for subjects to continue in a clinical trial. • Sponsors should provide additional information in the final clinical study report to the FDA. The report should include contingency measures that were put in place to manage study conduct during the COVID-19 crisis, a log of all trial participants affected by COVID-19 (to include subject ID, clinical site, and the deviation), the justification for the changes implemented, and the impact of the changes on the data results and safety.

more about this virus, the CDC and other governmental health authorities are issuing new guidance frequently.[2]

As described above, performing diagnostic or clinical research efficacy procedures presents even greater challenges especially when an aerosol generating procedure is involved. Some centers require COVID-19 testing within 48-72 hours of a procedure even with the understanding that an individual may be exposed or test positive within that period. PPE recommendations should be in place for all anticipated scenarios. While requirements may vary from one healthcare facility to another, it is generally accepted that full PPE (N-95 respirator masks in combination with a face shield, protective gowns, and gloves) must be worn by clinical or research staff when in the presence of COVID-19 positive individuals or when any individual (COVID-19 positive or unknown) is undergoing an aerosol generating procedure. Other recommendations from the CDC to minimize exposure include use of a closed private room, PPE required door signage, and allowing the room to remain empty for a period after the procedure to allow enough ventilation to clear the room of any remaining viral particles. Staff will need to keep the N-95 respirator mask in place while remaining in the room to complete follow-up tasks and disinfection of the room. Hand hygiene by both patients and staff should be done prior to entering and leaving the room (or for sedated patients upon discharge).

Guidelines regarding who should be tested for the COVID-19 virus have been provided, but confusion remains and the decision is ultimately at the discretion of the treating physician.[2] Industry sponsors are just now becoming aware that in order for research sites to begin to re-open their sites, COVID-19 testing may become a requirement for subjects as they are seen in-person for clinical visits as well as protocol-specified procedures. This raises questions such as where will testing be done and who bears the cost of the testing (the subject, industry sponsor, or the research site). Informed consents will need to be revised to add the new information as it will involve another procedure and possibly change the risk to the subject.[10]

THE FUTURE OF CLINICAL RESEARCH

"In the midst of chaos, there is also opportunity"– Sun-Tzu, The Art of War.

No one knows for sure when we will be able to get back to business as usual. Considering that an effective vaccine is not expected to be available for another 12-18 month, the probability that the virus will still be with us in 2021 and beyond is likely. Nevertheless, we must re-engage in clinical research. Interventional clinical studies involve the investigation of either a new drug, device, or other interventions for safety, efficacy, and/or long-term side effect profile. The patient populations targeted in these essential trials include oncology indications as well as nononcology indications (pulmonary, cardiovascular, renal, dermatology, neurology, surgical, etc.). Many of the patient populations targeted in these clinical trials suffer from medical conditions for which there is not an effective treatment. Currently, it is estimated that about 2.8 million participants are being sought to take part in clinical trials. Sadly, less than 10% of people participate; between 2015 and 2016, there were only 40,833 people in the United States participating in clinical trials.[11] This continuing resistance to participating in clinical studies must be overcome. The COVID-19 pandemic has further hindered the conduction of clinical studies. Yet, the pandemic has also promoted a surge in research directed at studying the condition. The impact of these 2 opposing forces is yet to be determined.

One way to change the landscape of clinical research is by incorporating more technology into the conduct of such studies. Many sites are already engaged in virtual recruitment via web-based study referral services. Healthcare facilities delivering telehealth services prior to the pandemic were able to reschedule patients to telehealth visits almost overnight. With the visitation restrictions in hospitals and long-term care facilities, IRBs/ECs began developing policies and processes for obtaining electronic informed consent including electronic signatures. The business world has been using electronic signatures for most of their legal documents for some time now and so have many research organizations. Importantly, it should be recognized that we no longer need to be in the same physical space to have investigator training meetings thanks to web-based applications that can accommodate large numbers of people for a virtual presentation. Centralized IRBs/ECs are already using a virtual meeting format. We can also adopt new technologies to reduce travel burden on subjects with the use of home monitoring technologies and the use of secure web portals for patient reported outcome questionnaires and diaries. While a number of procedures and assessments can be completed off-site, some will continue to require face-to-face contact, like collecting blood or other specimen samples.

The COVID-19 pandemic has emphasized the need for flexibility in conducting clinical research that cannot be done without human volunteers. Drastically reducing or halting important studies of diseases yet to be controlled or conquered is not an option. The COVID-19 pandemic will not be the last. We must be prepared to meet the next challenge quickly with the lessons learned from this pandemic, to adjust to unforeseen threats brought by the new challenge, and to promote relentlessly the preservation of human health and life.

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