

Navigating Clinical Trials in the Coronavirus Era.

- *COVID-19 is causing major upheaval around the globe, and the clinical trial industry is likely to face unprecedented challenges to business continuity. This analysis explores approaches for sponsors to mitigate risks to patient safety in ongoing clinical trials—both immediately and moving forward.*

The world is currently experiencing a global pandemic caused by the novel coronavirus SARS-CoV-2, which, as of the middle of March 2020 is known to have infected more than 125,000 people and resulted in nearly 5,000 deaths in more than 115 different countries. At least 1,300 cases have been confirmed in the United States, but due to limited testing so far, the number of actual cases of COVID-19 is almost certainly much higher, and is expected to rise significantly in the coming weeks and months.

This is a public health emergency and a humanitarian crisis that has already claimed thousands of lives. Most experts acknowledge that containment is no longer possible, and global health organizations are recommending measures that include restricting travel, working from home, limiting large public gatherings, and “social distancing” whenever possible. Governments worldwide have already enacted massive region- and country-wide restrictions on travel and movement in an effort to reduce spread of the virus. Large public events, including conventions, sporting events, and concerts, have been and continue to be cancelled.

Disruptions to business operations in all sectors have already been significant. This analysis deals with the specific impacts of the coronavirus outbreak on the clinical trial industry, and steps that pharmaceutical companies might take to mitigate risks to ongoing trials.

IMPACT ON CLINICAL TRIAL INDUSTRY

At any given moment, it is estimated that there are more than 40,000 ongoing global clinical trials, involving thousands of trial sites, tens of thousands of investigators, and hundreds of thousands of patients. These trials represent billions of dollars in expenditures and investment, and are critical to maintaining the pipeline of effective drugs and devices for both new and existing indications. An infectious epidemic event like the one the world is currently facing has the potential to threaten the continuity and success of these trials, with massive detrimental economic and human impact.

The traditional clinical trial model typically requires participants to report to a clinical site for scheduled study visits. Many patients will be legitimately concerned about going to a clinical site where they may have a dramatically increased risk of exposure to coronavirus. Many will worry about interacting with healthcare workers who themselves may have higher risks of exposure. Traditionally, participation in clinical research has often entailed both major and minor inconveniences for patients—arranging transportation, childcare, time off work, etc.—but has not necessarily come with additional health risks like COVID-19. Now that participants are being faced with these issues, sponsors must address them to protect both the patients and the healthcare staff who interact with them.

Technologies facilitating remote communication are currently being leveraged in business and personal contexts to reduce travel and person-to-person interactions. For example, the use of videoconferencing for business

meetings is recognized as an effective and affordable means to facilitate business continuity and reduce exposure to airports, crowds, colleagues, and handshakes. Pharma companies are already utilizing these solutions in place of physical meetings and conferences, but may not be implementing telehealth-based solutions when it comes to trial execution.

Incorporating telehealth into clinical trials and virtualizing study visits are strategic approaches that sponsors can take to reduce participant burden in completing study visits. Indeed, virtualizing trial operations to the greatest extent possible can help keep patients and study staff safe, support the wider public effort to slow viral spread, and provide business continuity to ensure optimal outcomes of ongoing and planned trials. This more patient-centric approach is also an effective way to reduce the burden on healthcare systems and personnel that may be dealing with overwhelming circumstances due to the pandemic crisis.

MITIGATION STRATEGIES IN THE CURRENT HEALTH CLIMATE

Trial sponsors need to understand their options and the approaches that may be available to them (apart from delaying start dates of trials or postponing study visits). Sponsors and their service providers need to quickly assess whether study protocol changes might be effective in mitigating any additional risks to participants caused by COVID-19, and how best to execute those changes.

Many of the study adaptations that a virtual trial model provides directly impact participant travel and movement.

Elements of the clinical trial life cycle that can be executed virtually—from recruitment to study closeout—are supported by software platforms that enable collection and storage of high-quality, centralized data in real time. Remote patient study visits can be conducted by study investigators via telemedicine, and mobile research nurses (if required) can visit patients at their homes to complete a variety of study procedures, in a manner that is most convenient to participants. In addition, study materials are shipped directly to the patient's home as appropriate. All of these approaches can help reduce the number of in-person clinic visits that are necessary in the traditional site-based model.

- **Employ a trial platform that enables and streamlines virtual visits.** A key element required to connect study teams with remote patients is the use of a powerful telemedicine-based virtual trial software platform, specifically designed to capture study data and to enable and coordinate workflows among trial team members regardless of their physical location. Comprehensive virtual trial platforms establish a centralized hub for trial activities such as electronic data capture, eConsent, ePROs, telemedicine visits, patient notifications, and more.
- **Leverage telemedicine-based physician visits.** The virtual trial model enables in-home study procedures that have traditionally required in-person interactions between a study investigator and participants at a clinical site. These virtual visits can include physical exams (facilitated by a mobile research nurse in the participant's home) and a variety of procedures and assessments that allow for the collection of endpoint data and clinician-reported outcome assessments.
- **Incorporate at-home nurse visits to replace clinic visits.** Mobile research nurses can be deployed to visit participants at home to collect blood/biospecimens, monitor vital signs, complete protocol-specified procedures and facilitate data capture. Patients may prefer one-on-one home visits with an individual healthcare professional who is following prescribed guidelines to ensure their health and safety, rather than having to travel to a research site or even a local lab for a blood draw.
- **Ship study supplies directly to the patient.** The virtual trial model incorporates convenience for the patient at various touch points throughout the journey, including the shipment of all study drugs and materials directly to the home. This step also eliminates much of the risk associated with the patient traveling to a research site to retrieve study materials required for their participation.

STUDY CHARACTERISTICS TO CONSIDER

When designing a trial that incorporates virtual elements, there is often a question of how best to balance virtual and in-person interactions. The desire and need to mitigate the additional risks posed by COVID-19 may provide further justification for the incorporation of virtual components of a clinical trial.

Sponsors should be mindful of several key considerations, among them:

- The disease severity and comorbidities of the patient population within a study. Does this population have traits that may put them at higher risk of developing a more severe manifestation of a coronavirus infection?
- How will data be collected during in-home study visits? Is it safe and feasible to reliably collect these endpoints in the patient's home? If so, can patients self-assess and report results electronically, or must a nurse or other clinical professional be present? What are the regulatory considerations of this in-home data collection?
- Can the investigational medicinal product be shipped, stored, and administered in the patient's home?
- Does the protocol include any procedures (e.g., tissue biopsies, imaging, etc.) that investigators must perform in a clinic?
- Can the investigator facilitate, guide, observe, or evaluate a specific procedure or evaluation through telemedicine or videoconferencing?

FLEXIBILITY IS KEY

Sponsors will face a complex and difficult decision-making process during this coronavirus crisis, one that justifiably prioritizes patient safety at a time when there is still emerging data as to how best to minimize the threat of exponential viral exposure and spread. At the same time, there will remain a need to achieve long-planned study timeline goals despite the unforeseen circumstances that have emerged. Although longer lead times and early planning are often the best approach when adapting a study to the virtual model, more rapid and agile adjustments to incorporate virtual components to trials threatened by this emerging global pandemic will likely be required.

When considering changes to active study protocols, it is important to note that FDA regulations allow for expedited changes when submitting amendments to IRBs that relate to immediate hazards to human subjects:

Each IRB shall ... (a) Follow written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects. 21 CFR 56.108(a)(4).

All IRBs should be continuously assessing the current situation and evaluating the coronavirus impact on human research trials, and many are recommending that sponsors take appropriate steps to determine whether any study procedures that require participants to travel to a hospital or a clinic can be eliminated or managed remotely. Changes and/or amendments to study protocols should be considered in this regard, with the recognition that "changes to eliminate apparent immediate hazards to human subjects" may be considered necessary and appropriate by the FDA.

CONCLUSION

The COVID-19 outbreak is a rapidly evolving situation, and there is still much that is unknown about the trajectory of infections worldwide and the ultimate global impact. It is clear, however, that all sectors must take steps to reduce the risk of viral spread and to maintain public health (particularly those who are the most vulnerable) in order to ensure social and business continuity.

Incorporating virtual visits into clinical trials is a logical approach to maintaining patient participation in ongoing and future clinical trials. The virtual trial model provides participants with direct and immediate access to investigators, nurses, and other study team personnel from home, which not only boosts engagement and retention, but may assuage some of the concerns patients have about participating in site-based research in the midst of a public health emergency.

Although sponsors—and the public at large—are currently experiencing a period of great uncertainty driven by the coronavirus, the current health landscape underscores the advantages of virtual trials in supporting public efforts to contain COVID-19 while ensuring the execution of ongoing and planned clinical research.