PG Briefing
November 22, 2021

Clinical Research in a Post–Pandemic World

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Several weeks into the COVID-19 pandemic, the U.S. Food and Drug Administration (FDA) and the Office for Human Research Protections of the U.S. Department of Health and Human Services (OHRP) issued guidance encouraging researchers to design and implement protocols, policies, and procedures (or revise existing ones) in a manner intended to protect study subjects to the greatest extent possible, not just from potential transmission of the SARS-COV-2 virus, but also from harm that may result from discontinuing trials or deviating from protocols in light of the challenges and restrictions caused by the pandemic.[1] As a result, research institutions, sponsors and other clinical research stakeholders began implementing a number of changes. Although the FDA and OHRP intended to illustrate how such interim flexibilities may work within the existing regulatory framework, some of these changes may remain fixtures of clinical studies in a post-pandemic world and could benefit from updated regulatory schemes or guidance. Until then, researchers and industry stakeholders will have carefully to assess which pandemic-era practices may continue in light of the potential costs, patient safety considerations, and other factors.

How the COVID-19 Pandemic Changed the Conduct of Clinical Studies
Electronic Consenting

One of the most conspicuous changes to the conduct of clinical research that arose as a result of the COVID-19 pandemic was the expanded use of electronic consenting (e-consenting) for study subjects. Under both FDA regulations and the federal policy for the protection of human subjects at 45 CFR Part 46 (the "Common Rule"), researchers are typically required to obtain informed consent from all study subjects before enrolling them in a clinical study.[2] Under both sets of rules, researchers must present each study subject with a specific set of information intended to enable the subject to evaluate the risks and benefits associated with their participation in the clinical study and obtain a signature from each subject confirming their understanding of the information presented, as well as their intent to enroll in the study.

Prior to the onset of the COVID-19 pandemic, industry preference and standard practice was to obtain informed consent in writing even though both FDA regulations and the Common Rule permit electronic signatures for such purpose. Since study subjects were often enrolled during in-person encounters, obtaining hard copies of informed consent documents did not typically necessitate an extra visit with each subject, and as explained in greater detail below, obtaining a written signature was often easier from a recordkeeping and validation standpoint. Early on in the COVID-19 pandemic, however, regulators, researchers, and industry stakeholders quickly identified the expansion of e-consenting for clinical studies as a viable method to reduce in-person contact between study subjects and research staff.

FDA and OHRP previously issued joint guidance on the use of e-consenting in 2016, which addressed, among other things, how to present electronic informed consent documents to study subjects, how to address a study subject's questions during the e-consenting process, and how to approach Institutional Review Board (IRB) approval and regulatory documentation requirements.[3] FDA's initial and updated guidance on conducting clinical studies during the pandemic reiterated and clarified guidelines provided in the 2016 joint guidance relating to the proper use of e-consenting in clinical studies.[4] To further promote the uptake of e-consenting, FDA even offered researchers use of a free e-consenting platform the agency developed in conjunction with academic and industry partners called the "COVID MyStudies" app.[5] As a result, the use of e-consenting present day remains a far more common practice in the clinical research community than it was in years prior.[6]

Remote Study Monitoring

Another strategy regulators, researchers, and industry stakeholders have embraced in an effort to reduce the need for unnecessary travel and in-person contact during the COVID-19 pandemic is the implementation of procedures for remote study monitoring and research administration.

Traditionally, sponsors and contract research organizations (CROs) with regulatory responsibility for monitoring the conduct of clinical studies have sent study monitors to clinical research sites to oversee study activities in-person and to review on-site study documentation for compliance with research protocols and applicable laws. Since many studies, especially those involving large study cohorts or populations with rare diseases, leverage multiple study sites in different, often distant, geographical areas, in-person study monitoring requires a significant amount of travel and can be costly.

Similarly, non-clinical research staff that provide administrative support for clinical research at institutions and other study sites traditionally worked on-site to promote coordination between researchers and institutional leadership, and to support the activities of visiting study monitors and other sponsor, CRO, or investigator personnel.

Stay-at-home orders and travel restrictions during the COVID-19 pandemic caused an almost immediate hold on the traditional conduct of study monitoring and administrative activities. Researchers and industry stakeholders responded by leveraging the remote access capabilities of electronic health record (EHR) software, teleconferencing, and other technologies to allow clinical research activities to continue with limited interruption. These technologies enable study monitors to review documentation electronically, and facilitate communication between study monitors, on-site clinical research staff, and administrative personnel working remotely. As businesses and institutions continue to weigh the risks and benefits of returning to the workplace and re-initiating business travel, remote access and communication technologies continue to play a pivotal role in the execution of clinical research.

Home Health and Telehealth Services

Just as some patients tended to forego routine medical care for fear of COVID-19 exposure in health care facilities, some research subjects were hesitant to return for study visits or enroll in clinical studies for the same reason.[7] For vulnerable populations in particular, the risk of COVID-19 transmission could outweigh the benefit of study participation. It therefore became important for purposes of study subject accrual and retention that researchers implement alternative methods of interacting with subjects, such as through home health services or telehealth visits.

OHRP's guidance indicated that it expected investigators to cancel or postpone non-essential study visits or conduct phone visits instead of in-person visits to reduce COVID-19 transmission risk during the public health emergency.[8] The FDA's guidance specifically outlined some considerations for researchers when implementing

home health and virtual services, including the limitations thereof.[9] For example, researchers should consider whether the specific storage and handling requirements of complex investigational products can be met through in-home administration. Likewise, telehealth and virtual assessments may not be feasible for protocols that require specific visualization of or interactions with the subject in a way that cannot be accomplished virtually.[10]

Researchers have begun to embrace home health services when possible, which not only reduces the risk of disease transmission for study subjects, but also reduces their travel burden and enhances their experience overall.[11] This could, in turn, improve clinical study participation and retention.[12]

The pandemic also saw an uptick in telehealth services, partly due to the easing of regulatory restrictions such as licensure requirements on rendering telehealth services across state lines and expanded coverage for such services. For example, many states broadened the definition of telehealth services (e.g., to include audio-only communications) and removed other limitations (e.g., such as requiring a pre-existing provider-patient relationship or in-state license).[13] State and federal actions also led to expanded coverage of telehealth services through Medicare, Medicaid, and commercial insurance plans.[14] Both home health services and telehealth services presented greater opportunity for researchers to interact with study subjects and enable studies to continue despite the pandemic.

Changes and Challenges Likely to Carry Forward

The ways in which researchers and regulatory authorities have responded to COVID-19 challenges may very well change research practices beyond the pandemic. For example, the increased utilization of e-consenting and the emphasis on remote study monitoring and research administration during the COVID-19 pandemic eliminated unnecessary in-person contact and the need for travel to study sites. Even after the pandemic, reduced in-person contact will continue to minimize logistical burdens. Further, continued emphasis on remote study monitoring and research administration will also have the added environmental and financial benefits of decreasing the need for travel from site to site.

That said, e-consenting processes and increased remote access to study records and materials represent an increased expense to study sites, different regulatory compliance challenges, and increased risk of data security incidents. While FDA is providing free access to its COVID MyStudy app during the COVID-19 pandemic, institutions wishing to implement their own e-consenting processes and infrastructure are faced with a number of expenses, including the upfront cost of implementing e-consenting software and hardware components that comply with applicable FDA and OHRP regulations (e.g., FDA 21 C.F.R. Part 11 e-signature and documentation requirements), research staff training on e-consenting processes, and remote study subject guidance and support. Similarly, providing study monitors with remote access to study records requires the implementation of EHR processes and security mechanisms that can represent additional expense for research sites, and create risk of data loss not similarly present through controlled, on-site review of study records.

As with e-consenting and remote study monitoring, the use of home health and telehealth services similarly reduce the risk of disease transmission, as well as the burdens of participating in clinical studies. For these reasons, they may also help with study subject accrual and representational disparities in clinical research study populations beyond the COVID-19 pandemic, consistent with greater efforts to increase diversity in clinical research.[15] Given that diversity and inclusion will be an important emphasis in clinical research going forward, so too should the pandemic-era methods that enhance access to clinical research and participation. Although promising in some respects, home health services may not be feasible for all studies, depending on the particular investigational drug or device. In addition, decentralized research services create supervision issues for investigators and study coordinators. Supervision is especially challenging where the home health agencies performing study services are engaged directly by CROs and sponsors. In light of these challenges, researchers would benefit from updated

regulatory guidance to help determine in advance whether a particular study involving home health visits will meet FDA requirements.

Additional regulatory changes, including those that would make flexibilities available during the public health emergency permanent, would make it easier to continue to incorporate telehealth services into research protocols. As state public health emergencies are either rescinded or allowed to expire, some states are making the pandemic-era telehealth flexibilities permanent by creating pathways for interstate licensure (either by adopting the interstate licensure compact or implementing an alternative registration processes for out-of-state providers) and expanding coverage of telehealth services.16 However, licensure and reimbursement laws still vary by state and are likely to remain in flux for the near future. Researchers will have to carefully assess applicable regulatory schemes before incorporating telehealth services in research protocols.

Exacerbating the logistical challenges posed by the COVID-19 pandemic, many research institutions additionally report significant shortages in study staff and large attrition among their research coordinators and other key personnel. Staffing shortages have led to material delays in the performance and completion of clinical studies and enhanced compliance risk as research institutions struggle to perform research compliance obligations with fewer study staff. Continued staffing shortages could also exacerbate supervision issues for investigators and oversight by in-house IRBs. Regulatory changes that promote safety and flexibility while easing compliance burden are all factors could help address transmission concerns and burnout.

Conclusion

While the changes and adaptations discussed above that research institutions, sponsors, and other stakeholders in the clinical research community have implemented in response to the COVID-19 pandemic were, in many cases, born of necessity, they are also welcome and modernizing developments. They represent a progression in accepted practices for the conduct of clinical research, facilitated by greater access to technology and changes in the way researchers interact with study subjects and those responsible for overseeing the research. As we hopefully begin to transition out of the COVID-19 pandemic, researchers and stakeholders must consider which practices are sustainable and with what investment (e.g. in enterprise-wide electronic data capture and e-regulatory binder systems that are 21 CFR Part 11 validated, enable remote monitoring and are associated with adequate data security controls). And OHRP, FDA, and other regulatory authorities should continue to consider the ways in which they can modernize applicable regulations and guidance to support a post-pandemic world, with an increasingly technology-driven and remote means of safely performing clinical research.

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[1] *See* FDA, *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*, 5 (Updated August 30, 2021, available at https://www.fda.gov/media/136238/download); OHRP, *OHRP Guidance on Coronavirus* (Rev. April 8, 2020, available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html).
[2] *See* 45 C.F.R. Part 46; 21 C.F.R. Part 50.
[3] *See* DHHS, *Use of Electronic Informed Consent Questions and Answers: Guidance for Institutional Review Boards, Investigators, and Sponsors* (December 2016, available at https://www.fda.gov/media/116850/download).
[4] *See* FDA, *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*, (Updated August 30, 2021, available at https://www.fda.gov/media/136238/download).
[5] *See* FDA, *COVID MyStudies Application (App)* (Updated May 29, 2020, available at https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app).

[6] *See, e.g.*, Jaton et al., *The Use of Electronic Consent for COVID-19 Clinical Trials: Lessons for Emergency Care Research During a Pandemic and Beyond*, 27 J. Acad. Emerg. Med. 1183-1186 (September 24, 2020); De Sutter et al. *Clinical Research in Neonates: Redesigning the Informed Consent Process in the Digital Era*, 9 Frontiers in Pediatrics 724431 (September 1, 2021).
[7] *See* Fleury, et al., *Association of the COVID-19 Outbreak With Patient Willingness to Enroll in Cancer Clinical Trials*, 7 J. Am. Med. Ass'n Oncology 131 (Jan. 2021), available at: https://jamanetwork.com/journals/jamaoncology/fullarticle/2772839.
[8] OHRP, *OHRP Guidance on Coronavirus* (Rev. April 8, 2020, available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html).
[9] *See* FDA, *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*, (Updated August 30, 2021, available at https://www.fda.gov/media/136238/download.
[10] *See id.*
[11] *See* Bryant, *Home Health to Play Increasingly Important Role in Clinical Research*, Home Health News (Aug. 3, 2020), available at: https://homehealthcarenews.com/2020/08/home-health-to-play-increasingly-important-role-in-clinical-research/.
[12] *See id.*
[13] *See* Weigel, et al., *Opportunities and Barriers for Telemedicine in the U.S. During the COVID-19 Emergency and Beyond*, available here: https://www.kff.org/womens-health-policy/issue-brief/opportunities-and-barriers-for-telemedicine-in-the-u-s-during-the-covid-19-emergency-and-beyond/; *see also* Shachar, et al., *Implications for Telehealth in a Postpandemic Future*, 323 J. Am. Med. Ass'n 2375 (Jun. 16, 2020), available here: https://jamanetwork.com/journals/jama/fullarticle/2766369.
[14] *See* Weigel, et al.; *see also* Shachar, et al.
[15] *See, e.g.*, FDA, *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry* (November 2020, available at https://www.fda.gov/media/127712/download); OHRP, *Consideration of the Principle of Justice under 45 CFR part 46 Secretary's Advisory Committee on Human Research Protections* (July 22, 2021, available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-consideration-of-the-principle-of-justice-45-cfr-46.html).
[16] *See* Dooley, et. al., *Post COVID-19 Rollbacks in Telehealth Laws and Regulations Makes Compliance Difficult Across All Fifty States*, Am. Bar Ass'n (Sept. 22, 2021).

