The Coronavirus (COVID-19) pandemic presents significant challenges for clinical trial sponsors. The US Food and Drug Administration issued guidance on March 19, 2020, that provides greater flexibility to adjust clinical protocol and to use telemedicine platforms and virtual clinical sites.

IN DEPTH

On March 19, 2020, the US Food and Drug Administration (FDA) issued Guidance for Industry, Investigators, and Institutional Review Boards on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic to address concerns related to the Coronavirus (COVID-19) pandemic. COVID-19 may pose significant challenges to sponsors conducting clinical trials, and FDA outlines considerations to assist sponsors in “assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic.” Highlights of this guidance include greater flexibility to implement COVID-19-related clinical protocol changes without prior FDA or
institutional review board (IRB) authorization and increased use of telemedicine platforms and virtual clinical sites.

FDA recognizes that many clinical trials require study participants to visit a designated hospital, clinic, physician office or other clinical trial location to receive investigational drugs or devices or undergo regular protocol-specific medical examinations to monitor various outcomes during the trial. For most studies, the protocol prescribes the timing, frequency and manner of execution for these activities and requires that they be performed by clinical trial investigators or other appropriate team members. Deviations from the protocol may affect patient safety, outcomes and the validity of clinical trial data. Consequently, the IRB, FDA or both must approve any significant deviations prior to implementation. However, the COVID-19 public health emergency and social distancing protocols, present critical challenges for clinical trial sponsors, investigators, IRBs, participants and clinical trial sites and, in the absence of FDA guidance, would require many or most protocols to be amended.

**Documentation of COVID-19 Protocol Changes**

FDA’s guidance reflects a flexible, risk-based approach to clinical trial human subject protection, record-keeping and data integrity requirements. It aligns with the approaches announced by FDA’s international counterparts, such as the United Kingdom’s Medicines and Healthcare Products Regulatory Authority (MHRA). For example, on March 12, 2020, the MHRA issued advice regarding conducting clinical trials given COVID-19-related challenges, referencing similar issues as FDA, such as travel restrictions and quarantines.

Like MHRA, FDA allows for changes to the protocol or investigational plan without IRB approval or before filing an amendment to the investigational new drug (IND) or investigational device exemption (IDE) application if the changes are implemented in order to “minimize or eliminate immediate hazards or to protect the life and well-being of research participants.” FDA does not define what constitutes an “immediate hazard,” but it provides “to limit exposure to COVID-19” as an example of such a hazard. Sponsors should seek IRB input on defining what circumstances within a particular trial may constitute an immediate hazard and should inform the investigators. Definitions should be specific but also provide flexibility (e.g., a discretionary or catch-all category for unforeseen or unpredictable circumstances).

Sponsors should apply rigorous documentation standards for COVID-19 scenarios, as FDA expects appropriate reporting, documentation and justifications after-the-fact. FDA expects sponsors to include the following information in the relevant sections of the clinical study report:

- “Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures”

- “A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual’s participation was altered”

- “Analyses and corresponding discussions that address the impact of
implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.”

FDA also recommends that sponsors engage the IRB or independent ethics committee (IEC) as early as possible regarding anticipated protocol or investigational plan changes. IRBs or IECs should develop proactive procedures to address documentation issues. These include reporting deviations, with a priority on those that may affect the safety of study subjects.

**Use of Alternative Methods for In-Person Visits**

FDA states that it is willing to consider alternatives for administration of investigational products that are normally administered by a healthcare provider, where appropriate (e.g., home nursing, use of non-study personnel). Regardless of how the investigational product is provided to trial subjects, sponsors must ensure that study personnel follow regulatory requirements surrounding investigational product accountability, distribution and documentation. To implement such requirements, sponsors may need to discuss with healthcare providers, clinical sites and other third parties which entities/stakeholders will take responsibility (financial and otherwise) for these steps, and amend contracts and other documentation accordingly. To the extent that these new relationships and collaborations require updated budgets, fair market value opinions, changes to the informed consent or HIPAA authorization (because of additional disclosures of protected health information or new recipients thereof) or other considerations, sponsors should take care to address and implement these compliance steps. Doing so may raise concerns from a healthcare provider or sponsor standpoint. For example, providers and sponsors should consider how the alternative administration methods may affect billing to, and payment by, health insurers for patient care incurred in connection with the trial.

FDA also encourages appropriate use of telemedicine platforms and virtual tools as alternative methods for site visits mandated by the protocol. Use of these alternative methods may raise privacy concerns that could require IRB review or new agreements with telemedicine providers. Sponsors also may need to include adequate information to demonstrate that the telemedicine platform is appropriate for clinical research purposes (e.g., appropriate access controls, use of consumer-based mobile platforms available to consumers to link to telemedicine platform).

Many telehealth or remote monitoring vendors offer solutions that are commercially available and have pre-existing, standard terms of use/privacy policies (TOU/PP). These documents often contain data use and privacy provisions and the ability to amend such terms at will. Such terms are likely contrary to typical informed consent language that (1) carefully specifies the permitted uses and disclosures of data and strict privacy protections, and (2) requires IRB review and approval before such practices can be changed (often requiring re-consenting subjects). Informed consent forms may need to be updated to indicate that the TOU/PP of deployed remote technologies will control in the event they conflict with the informed consent form provisions. Further, TOU/PP documents may reserve ownership of entered data to the
vendor (because these are typically consumer-facing tools), and sponsors should carefully review the documents to account for these issues.

The US Department of Health and Human Services Office for Civil Rights (OCR) issued a statement on March 17, 2020, that it will exercise its enforcement discretion and waive potential penalties against covered healthcare providers that use non-HIPAA-compliant remote monitoring and telehealth tools during the national emergency to provide telehealth treatment, discussed in depth here. It is not clear from OCR or FDA guidance whether clinical research falls within the scope of this enforcement discretion. In certain cases, health systems serving as research sites may already have telehealth and remote monitoring solutions that can be leveraged to assist sponsors. Sponsors should confirm on whose behalf such vendors are working, and relative roles, rights and responsibilities for such technologies.

Sponsors planning to digitize information gathered during the clinical trial process and implement electronic signatures and records must ensure compliance with FDA’s electronic records regulations, detailed in 21 CFR Part 11. These regulations provide “criteria under which FDA considers electronic records, signatures, and handwritten signatures executed to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.” See 21 CFR § 11.1. These regulations apply to electronic systems used in the clinical trial setting, including electronic systems owned or managed by sponsors as well as electronic systems outsourced by the sponsor. The types of records that would need to comply with these regulations include:

- records required for clinical investigations of medical products that are maintained in electronic format in place of paper format, including all records that are necessary for FDA to reconstruct a study;
- records required for clinical investigations of medical products that are maintained in electronic format and where the electronic record is relied on to perform regulated activities;
- records for clinical investigations submitted to FDA in electronic format under predicate rules, even if such records are not specifically identified in FDA regulations; and
- electronic signatures required for clinical investigations intended to be the equivalent of handwritten signatures, initials, and other general signings.


**COVID-19 Screening**

Sponsors should consider protocol changes to address COVID-19 screening of trial participants, investigators and study personnel. If a trial site is a healthcare system or a hospital, it may require subjects to undergo additional COVID-19 screening before visiting the site. Trial subjects should be informed of this requirement, and sponsors might need to amend informed consents accordingly. Sponsors should also implement COVID-19 screening or related safety protocols for study personnel who have physical contact with subjects during the trial. This may include the use of protective garments (e.g., masks, gowns) during intake, examinations or dosing.
Sponsors should assess whether and how these additional measures may affect trial design or outcomes. FDA states that screening procedures mandated by a healthcare system or hospital do not need to be reported as protocol amendment, unless the sponsor will use this data as part of a new research objective.

While the FDA guidance presents a reasonable approach to addressing COVID-19 complexities and encourages stakeholders to contact FDA with specific questions, it does not describe the precise mechanisms for engaging with FDA. The absence of clarity on this point raises questions regarding FDA’s allocation of resources to respond to sponsor questions in a timely manner. This is a concern for sponsors given the significant volume of ongoing clinical trials (FDA’s recent report for the Center for Drug Evaluation and Research reorganization lists a backlog of more than 10,000 applications with Prescription Drug User Fee Act deadlines) and the current lack of current to facilitate rapid responses in a constantly evolving public health emergency. Traditional meetings with FDA typically require sponsors to wait 30 days after the meeting before obtaining information from FDA. See, e.g., FDA’s Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants (May 2009).

FDA has established dedicated email portals where industry and stakeholders can receive rapid responses (typically within 24 hours) to various COVID-19-related questions. Implementing a similar FDA email portal for clinical trial sponsors, sites, investigators and clinical research organizations would be a practical way to triage general COVID-19 clinical trial questions, but it may be of limited value to provide rapid responses to the fact-specific questions that typically arise in clinical trials. In the absence of specific feedback from FDA, sponsors should engage IRBs and document protocol changes with sound evidence and appropriate clinical justifications.

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