Conduct of Clinical Trials During the COVID-19 Pandemic: Recommendations from FDA

by Alexander Varond, Julie Tibbets

As the COVID-19 pandemic unfolds, our drug, biologic, and medical device clients conducting or planning to conduct clinical trials may be faced with challenges related to quarantines, travel limitations, site closures or access restrictions, infection transmission concerns of site research personnel and study subjects, and supply chain interruptions. Nonetheless, it remains critical during the COVID-19 pandemic to continue to assure the safety of trial participants, comply with good clinical practice (GCP) requirements, and minimize risks to trial integrity. In this client alert which follows our earlier article on product development considerations for COVID-19 and article on FDA scrutiny of COVID-19 medical product marketing, we briefly discuss the impact the COVID-19 pandemic may have on our life sciences clients, and we provide an overview of FDA's "Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" issued on March 18, 2020 ("COVID-19 CGP Guidance Document"; linked here).

The impact of COVID-19 illness and control measures will vary on a number of factors, including the nature of the disease being studied, trial design, and the region(s) in which the study is being conducted. Notably, the impact may include difficulties meeting protocol-specified procedures, including administering or using the investigational product, or adhering to protocol-mandated visits and laboratory/diagnostic testing. Consequently, protocol modifications may be required and protocol deviations may be unavoidable due to COVID-19.

FDA, with joint recommendations from its drug, biologic, and medical device centers along with its Office of Good Clinical Practice, released today helpful guidance to industry highlighting the Agency's recommendations to sponsors and investigators conducting clinical trials and institutional review boards (IRBs) and independent ethics committees (IECs) overseeing those trials. Given the public health emergency and its immediate impact on current or planned clinical trials, FDA released the COVID-19 GCP Guidance Document as a final guidance prior to seeking public comment. It is being implemented immediately and affects medical products regulated by the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH).

In its COVID-19 GCP Guidance Document, FDA succinctly sets forth the Agency's expectations and reaffirms its requirements relating to GCP:

Robust efforts by sponsors, investigators, and IRBs/IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. . . . FDA recognizes that protocol modifications may be required, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, will be important.

In addition, the general theme that comes through from FDA's guidance document is that the Agency appreciates the significant and possibly long-term impact COVID-19 may have on clinical trials. In many ways, the COVID-19 GCP Guidance Document feels like an opening move on the part of FDA to tackle the impacts of the COVID-19 pandemic across medical product development while also acknowledging the fluidity of the public health crisis and the case-by-case nature of COVID-19 impacts on clinical trials and their sponsors.

The Agency's recommendations in the COVID-19 GCP Guidance Document are broadly organized into three sections. The first applies to ongoing trials; the second applies where policies and procedures for COVID-19 have not already been put in place; and the last section applies to all clinical trials, given its focus on the requirements related to documenting in clinical study reports the impact of COVID-19. The following bullets represent helpful excerpts from the COVID-19 GCP Guidance Document.

I. CONSIDERATIONS FOR ONGOING TRIALS

As sponsors consider subject safety, FDA recommends they focus on the following:

- Subject safety; informing subjects of changes. Safety of trial participants is paramount. Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Trial participants should be kept informed of changes to the study and monitoring plans that could impact them.
- Decisions on subject participation. Sponsors should consult with IRBs and IECs to determine whether subject safety is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial.
- Alternative safety assessment methods. Sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented.
- Additional safety monitoring, if investigational product or site is unavailable. In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., withdrawal of an active investigational treatment).
- Documenting COVID-19 screening. COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.
- IRB/IEC engagement & immediate hazard to subjects exception. Sponsors and clinical investigators are encouraged to engage with IRBs/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the IND or IDE, but are required to be reported afterwards.
- Implementing and documenting changes. The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted. I
- Documenting missing data. It will be important to capture specific information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).
- Administration, delivery, and accountability of investigational products. Sponsors should evaluate alternative secure delivery methods. If investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended. Maintaining investigational product accountability is required, as before the COVID-19 pandemic, and should be addressed and documented.
- Efficacy assessment changes and documentation. With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible.

- Changes to study protocols and statistical analysis plans. If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses.
- Clinical trial monitoring. If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites.

II. RECOMMENDED ACTIONS IF POLICIES AND PROCEDURES ARE NOT ALREADY IN PLACE

Sponsors, clinical investigators, and IRBs should consider establishing and implementing policies and procedures, or revising existing policies and procedures, to describe approaches to be used to protect trial participants and manage trial conduct during possible disruption of trials as a result of COVID-19 control measures at study sites. Changes to policies and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s). Depending on the nature of the change, a protocol amendment may be required.

III. FOR ALL TRIALS IMPACTED BY COVID-19: CLINICAL STUDY REPORT DOCUMENTATION

In the clinical study report or in a separate study-specific document, sponsors should document contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures, provide documentation at the subject level related to study disruption; and address the impact of contingency measures on the safety and efficacy results reported for the study.

IV. CONCLUSION

Today's guidance document represents an important kickoff of FDA's effort to address the concerns facing our life sciences clients. We will continue tracking these and other COVID-19-related issues as they unfold. Contact Goodwin FDA members Julie Tibbets or Alexander Varond for any questions related to conduct of clinical trials during the COVID-19 pandemic.

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Please visit Goodwin's **Coronavirus Knowledge Center**, where firm lawyers from across the globe are issuing new guidance and insights to help clients fully understand and assess the ramifications of COVID-19 and navigate the potential effects of the outbreak on their businesses.

CONTACTS:

Alexander Varond
Associate
+1 202 346 4064
avarond@goodwinlaw.com

Julie Tibbets
Partner
+1 202 346 4226
jtibbets@goodwinlaw.com
