

FDA Releases Updated Guidance on Clinical Trial Conduct During COVID-19 Pandemic

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Food, Drugs, and Devices

On March 27, the U.S. Food and Drug Administration (FDA) updated its guidance entitled “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic” (Updated Guidance).¹ A summary of FDA’s original guidance on this topic is available [here](#). The Updated Guidance preserves the content in the original guidance and adds an appendix that answers questions FDA has received about conducting clinical trials during the pandemic. As is the Agency’s policy for all COVID-19 related guidance documents, FDA is implementing the recommendations in the Updated Guidance immediately, without prior public comment. Interested parties may still submit comments about the Updated Guidance for consideration by the Agency.

The Appendix addresses the following questions:

- **What factors should a sponsor consider when deciding whether to suspend or continue an ongoing study, or to initiate a new study?**

The Updated Guidance makes clear that a sponsor’s primary consideration in determining whether to suspend or continue an ongoing study should be the safety of clinical trial subjects. Specifically, FDA recommends that sponsors work with IRBs/IECs to assess whether the continuation or suspension of a given clinical trial best protects the safety of clinical trial subjects.

The Updated Guidance then suggests several factors a sponsor should consider in making these assessments. Among other factors, sponsors should assess whether COVID-19 presents new safety risks to protocol implementation, and whether these risks can be mitigated; the availability of clinical investigators and trained clinical trial support staff to oversee the trial and manage safety issues; the supply of investigational product and other clinical trial supplies; the availability of information technology systems and other technological tools to support the trial; and whether it is feasible to conduct the trial in light of any federal or state COVID-19 public

¹ The Updated Guidance is available at <https://www.fda.gov/media/136238/download>. The Oncology Center of Excellence has been added as an author.

health measures. FDA also recommends that sponsors consider the assessment of a study's Data Monitoring Committee (DMC), to the extent a DMC has been established.

FDA notes that the risk-benefit calculation of continuing a trial likely is different than a decision to initiate a trial. The Agency recommends that sponsors carefully consider their ability to mitigate risk to patient safety and ensure data integrity, as well as whether initiating a trial could interfere with government countermeasures to control COVID-19.

- **What factors should a sponsor consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to a trial participant?**

FDA recommends that sponsors consider “context-dependent issues” when deciding whether to continue administering or using an investigational product that appears to be providing benefit to a trial participant. These context-dependent issues include the seriousness of the disease or condition, whether reasonable alternative treatments are available, and the risks involved in switching treatments. In some cases, e.g. interruption of supply, it may be necessary to stop administering the investigational product in a trial. Where such discontinuation might present substantial risk to certain subjects (e.g., those perceived to be benefitting clinically), FDA recommends that the sponsor, after discussion with the relevant review division, “consider amending the protocol . . . to limit investigational product use to those patients with apparent benefit and discontinue investigational product use to other participants.”²

- **How should sponsors manage protocol deviations and amendments to ongoing trials?**

FDA continues to recommend that sponsors document specific COVID-19 related protocol deviations and the reasons for each such deviations. In the Updated Guidance, FDA expands on this recommendation, stating that it will permit sponsors to use alternative approaches to document protocol deviations given the expected increase in volume. For example, if study visits shift to telephonic/video contact rather than site visits, documentation that lists all such study visits (e.g., listing study reference number, patient ID, date of visit) generally would be acceptable.³

FDA regulations require submission of a protocol amendment for changes that significantly affect the safety of subjects (for phase 1 studies) or that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study (phase 2 or 3 studies). As FDA explained in the original guidance, protocol amendments that are necessary to prevent imminent hazards to patients may be implemented immediately, with subsequent submission and approval by the IRB and notification to FDA. Protocol amendments that are not required to prevent imminent safety risks to patients should be implemented after they are submitted to FDA and receive IRB approval. FDA will permit sponsors to consolidate several protocol modifications into a single protocol amendment so long as this is done expeditiously.

² Updated Guidance at 11.

³ *Id.* at 11.

The Updated Guidance specifies that an IND protocol amendment is not required when pausing enrollment in a trial to decrease potential exposure to COVID-19.

For studies under an IDE, while FDA generally must pre-approve changes to the investigational plan, certain changes can occur without prior approval, provided the sponsor provides notice to FDA within 5 days of implementing the change. FDA recognizes it may be challenging to submit 5-day Notices within the required timeframe, and will permit sponsors to consolidate implemented changes when submitting 5-day Notices and update the IDE as soon as possible.

- **How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 pandemic?**

The Updated Guidance provides specific language that sponsors should include in the subject line of the cover letter submitting a protocol amendment to FDA. Such submissions should contain a tracked changes version of the protocol to facilitate FDA review. For INDs, if FDA input is sought prior to implementation of the change to the protocol, the sponsor should indicate this in the cover letter.

- **Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA, if these visits are necessary for the safety of the trial participant and remote monitoring will not impact data integrity?**

FDA recognizes that in some cases it may be necessary to convert patient safety monitoring visits from on-site visits to virtual clinical trial visits in order to eliminate apparent immediate safety hazards posed by COVID-19. In this instance, a protocol change can be implemented before IRB review and approval and notification to FDA.⁴ Until the amendment is approved, these changes will constitute protocol deviations and should be documented as such. When conversion to remote monitoring results in missed protocol-required procedures, sponsors must evaluate the potential impact on patient safety and consider how best to mitigate that risk. In some cases, this may require that the sponsor discontinue the investigational product.

- **What is the best way for sponsors and investigators to capture changes in clinical trial conduct that may occur due to the COVID-19 pandemic?**

As in the original guidance, FDA recommends that sponsors and investigators capture specific information for individual participants that explains the basis for missing information and the relationship to the pandemic (e.g. from missed study visits or study discontinuations due to COVID-19). If the information cannot be captured in case report form(s), sponsors may develop processes that enable systematic capture of these data across sites so long as the process enables appropriate analysis of the data upon submission to FDA. Sponsors can also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations.

- **Can a sponsor switch to home delivery of a self-administered investigational product without amending the protocol?**

⁴ *Id.* at 13.

According to the Updated Guidance, if the protocol specifies pharmacy dispensing of an investigational product for self-administration by patients, a protocol amendment would be required to permit a switch to home delivery.⁵ Such a switch would only be appropriate if it does not raise new safety risks. Where direct-to-patient shipment is only contemplated for a discreet subset of subjects in a clinical trial, protocol deviations may be acceptable as an alternative to a protocol amendment. In all cases, the requirements for maintaining required investigational product storage conditions and investigational product accountability remain, and must be addressed and documented.

- **Can a sponsor switch to home infusion if participants are currently receiving an investigational product infusion at the clinical trial site?**

For infusion products, FDA directs sponsors to consult the appropriate FDA review division regarding plans for alternative sites for administration. This is particularly important for complex products (e.g., cellular and gene therapy products) where changes to storage and handling could adversely impact the investigational product. Sponsors must address and document applicable requirements for maintaining required investigational product storage conditions, reconstitution specifications, and accountability. When suitable alternative arrangements cannot be made, it may be appropriate to discontinue investigational product treatment while continuing study participation, albeit with potentially delayed assessments.

- **What are FDA's expectations regarding delays to on-site monitoring?**

To maintain participant safety and data quality and integrity, sponsors should try to find alternative approaches to on-site visits, such as: enhanced central monitoring; telephone contact with the sites to review study procedures, trial participant status, and study progress; or remote monitoring of individual enrolled trial participants. Sponsors should carefully document situations where monitors were unable to access, or had to delay, monitoring of a clinical site. This is particularly important where delay in accessing, or inability to access, study sites may have resulted in delayed identification of significant GCP non-compliance and/or protocol deviations.

- **How do I obtain a signed informed consent from a patient who is in isolation and the COVID-19 infection control policy would prevent us from removing a document signed by the patient from their hospital room?**

The Updated Guidance outlines several alternative procedures that would satisfy the informed consent documentation requirement if the patient signing the informed consent is in COVID-19 isolation. These include electronic means of obtaining informed consent, and processes of obtaining verbal informed consent from the patient over the phone paired with the documentation of a patient's signature of a physical informed consent document.

⁵ *Id.* at 14.

For further questions on clinical trial conduct during the COVID-19 pandemic, FDA has provided the following email address: Clinicaltrialconduct-COVID19@fda.hhs.gov.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Anti-corruption/FCPA practice:

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To best advise our clients on the rapidly evolving public health situation in the U.S., our [COVID-19 task force](#) is staying abreast of daily developments and tracking the latest federal, state and local policies related to COVID-19.

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