New Q&A Appendix to FDA Guidance on Clinical Trials during COVID-19

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As the ground keeps shifting, we are writing to update you on the U.S. Food and Drug Administration's (FDA) additions to the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (as updated, the Guidance). FDA originally released the guidance on March 18, 2020, as final guidance without comment. We commented on the original guidance here. FDA retained the main body of the original guidance and added an appendix of questions and answers. In the Q&A, FDA provides granular detail and examples of how to proceed with clinical trials during COVID-19. This Update discusses the Q&A.

Whether to continue an ongoing study or initiate a new study:

Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 pandemic?

Answer 1 (A1): A1 reiterates that study subject safety is paramount; sponsors will need to make decisions about the study in consultation with the investigators and IRB; and the decisions "will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease."

The Guidance advises Sponsors to "carefully consider" 8 bullet points when assessing whether and how to proceed with a clinical trial. These bullet points organize and expand upon concepts contained in the main body of the Guidance and add new considerations. We recommend reading the 8 bullet points.

A data monitoring committee (DMC) can provide support for these assessments. The DMC's assessment of changes to the study due to COVID-19 " is important to consider."

The risks and benefits of continuing an ongoing study vs. starting a new study (other than for COVID-19) are different. The Guidance lists a number of factors that, in our view, caution against initiating a study (e.g. impacts on investigators, staff, supply chain). FDA notes that "It is important to consider whether initiation of the trial could interfere with public health measures implemented by Federal and State authorities to control the virus."

Whether to keep administering/using the investigational product:

Q2. What key factors should sponsors consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to the trial participant during the COVID-19 pandemic?

A2: Considerations include:

– Does the subject appear to be benefiting from the treatment?

– Are there reasonable alternative treatments?

– Seriousness of disease or condition being treated.

– Risks involved in switching to alternative treatment.

If you need to discontinue use of the investigational product (e.g. supply chain issue or cannot ensure safe use/administration), there may be subjects for whom stopping the product might present a substantial risk (i.e. subjects whom the investigator perceives as having a clinical benefit). For that situation, sponsors should consider amending the protocol, after discussion with FDA, to limit the product to those individual subjects and to stop the product for the other subjects.

If subjects are discontinued from an investigational therapy, appropriate management after discontinuation is important.

Protocol deviations and amendments:

Q3. How should sponsors manage protocol deviations and amendments to ongoing trials during the COVID-19 pandemic?

A3: For protocol deviations necessitated by COVID-19, document the specific deviation and the reason. Given the large number of expected deviations, sponsors can consider alternative documentation approaches. The Guidance includes examples of information to include when switching from on-site visits to phone/video visits .

For study-wide protocol changes to prevent imminent hazards or to protect the life and well-being of subjects, the sponsor should make these changes, and then submit to the IRB for formal approval and notify the FDA through a protocol amendment to the IND or IDE.

A3 also provides details about whether pausing enrollment under an IND due to COVID-19 "significantly affects" safety under 21 CFR 312.30(b), how to consolidate and report protocol amendments not required to prevent imminent safety risks, and difficulties around meeting the 5-day notice under an IDE.

Submitting protocol changes:

Q4. How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 pandemic?

A4: For IND studies, sponsors should submit a formal amendment to the IND. The Guidance provides specific information to be included in the cover letter subject line.

For IDE studies, sponsors should submit an IDE supplement. The Guidance provides specific information to be included in the cover letter subject line.

For both, sponsors should include a tracked changes version of the protocol.

Virtual study visits without contacting FDA:

Q5. Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of the trial participant and it will not impact data integrity?

A5: The Guidance reiterates that switching on-site to virtual study visits, such as by phone or video, for safety reasons can implemented immediately, with later review by the IRB and notification to FDA. These are protocol deviations (until the amendment is approved), and documentation as described in A5 of the required deviations would generally be acceptable ("i.e., a document that lists each deviation (study reference ID, patient ID, and date))." A5 goes into further detail about information to include in the documentation.

A5 reminds sponsors that changing to phone or video visits would likely result in certain protocol-required procedures not being conducted (e.g. vital signs, blood samples for safety lab studies), and that sponsors should evaluate the potential safety impact and how to mitigate the risk.

For IDE Studies, FDA recognizes that sponsors may not be able to meet the 5 working day deadline for reporting deviations. "Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible."

Capturing deviations to address patient safety:

Q6. With the rapid changes in clinical trial conduct that may occur due to the COVID-19 pandemic, including multiple deviations to address patient safety, what is the best way for sponsors and investigators to capture these data?

A6: "It is important to capture specific information" for individual subjects that includes the reason for the missing information and the relationship to COVID-19. If it is not possible to capture this information in the case report forms, sponsors may develop processes for systematic capture across the sites in a way that facilitates analysis by FDA. "Sponsors may also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations."

Home delivery of investigational product:

Q7. If patients are currently dispensed investigational product through a pharmacy for self administration at home, can a sponsor switch that to home delivery without amending the protocol?

A7: Yes, if it would not raise new safety risks, but FDA regulations for investigational product storage conditions and product accountability continue and must be documented. A protocol amendment is required. If home delivery will be

implemented for some, but not all, study subjects, A7 addresses how to document this. Changes to the study product distribution mechanism would be part of a "cumulative" amendment of accrued changes, not an urgent protocol change.

Home infusion:

Q8. If patients are currently receiving an investigational product infusion at the clinical trial site, can a sponsor switch to home infusion?

A8: Sponsors should consider the safety risk to subjects who would miss an infusion. In general, FDA should be consulted first. Consultation is "strongly advised" for complex investigational products like cellular therapy or gene therapy products because of potentially altered storage and handling.

Storage condition, product reconstitution and product accountability requirements must be followed and documented.

Discontinuing product treatment, while continuing study participation with delayed assessments, may be appropriate.

On-site monitoring delays:

Q9. Considering that there will be likely delays to on-site monitoring of clinical trials during the COVID-19 pandemic, what are FDA's expectations in such circumstances?

A9: FDA recognizes that monitoring on-site may be delayed and encourages sponsors to find alternative approaches, such as enhanced central monitoring; phone calls with sites to review study procedures, subject status and study progress; or remote monitoring of individual enrolled subjects.

Because delays in on-site monitoring may result in delayed identification of GCP non-compliance (including major protocol deviations) at the site (including protocol deviations not due to COVID-19), sponsors "should carefully document situations where monitors were unable to access, or had to delay, monitoring of a clinical site ." The documentation of issues identified during monitoring should "indicate whether the delayed identification was due to postponed monitoring . FDA recognizes that unique situations at clinical sites will occur due to COVID-19 control measures and will consider these circumstances when evaluating inspectional observations ."

Informed consent from patient in isolation:

Q10. 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?

A10: The Guidance recommends the following detailed steps for consenting a patient in isolation if electronic consent is not possible (If available, electronic consent technology should first be considered (consistent with FDA's 2106 guidance on electronic informed consent)).

1. Health care worker enters patient's room and provides unsigned consent form.
2. If direct communication with patient is not feasible or safe, conduct a three-way audio or video call with the patient, an impartial witness, and investigator (or designee). Include additional participants requested by the

patient.

3. To ensure consistency across patients, follow a standardized process for conducting the informed consent process. Because you need to create and document this process in advance, we recommend that you review the steps outlined in A10 (see item #3).

Given the patient's isolation, "If the signed informed consent form cannot be collected and added to the study records, FDA considers the following two options acceptable to provide documentation that the patient signed the informed consent document:

1. Attestations by the witness who participated in the call and by the investigator that the patient confirmed that they agreed to participate in the study and signed the informed consent OR
2. A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient.

A copy of the informed consent document signed by the investigator and witness should be placed in the patient's trial source documents with a notation by the investigator of how the consent was obtained, e.g. telephone.

The trial record at the investigational site should document how it was confirmed that the patient signed the consent form (i.e., either using attestation by the witness and investigator or the photograph of the signed consent).

The note should include a statement of why the informed consent document signed by the patient was not retained, e.g., due to contamination of the document by infectious material."

If consent will be provided by a legally authorized representative because the patient is unable to provide informed consent, the investigator must follow the informed consent regulations.

FDA plans to update the appendix as new questions arise.

Access the FDA Guidance.

Access our Update on the main body of the Guidance.

If you have any questions or would like more information about these developing issues, please contact the following:

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