FDA ISSUES GUIDANCE ON COVID-19 DISRUPTIONS TO CLINICAL TRIALS

On March 18, 2020, the FDA issued FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic that provides guidance for Sponsors, Clinical Investigators and Institutional Review Boards ("IRBs") on how to address disruptions in the conduct of clinical trials ("Trials") as a result of COVID-19.

COVID-19 DISRUPTIONS TO CLINICAL TRIALS OF MEDICAL PRODUCTS

COVID-19 is having an unprecedented impact on the United States' health care system, including to both the participants in human clinical research and the facilities where Trials are held. The FDA notes that COVID-19, and the public health response to the virus, may result in the following disruptions to Trials, among other things:

- Changes to Trial protocols and resulting effects on informed consent, study visits and procedures, investigational product dosing schedules, data collection, study monitoring and adverse event reporting;
- Missing or incomplete information as a result of participant withdrawals due to safety concerns, social distancing, travel limitations and quarantines or missed visits;
- Supply chain interruptions as resources are diverted away from the preparation of investigational products;
- Potential quarantine or infection of Trial participants; and
- Changes in the clinical investigator, site staff or monitors due to travel restrictions.

FDA RESPONSE TO IMPLICATIONS

The FDA recognizes that COVID-19 disruptions may result in "unavoidable protocol deviations." In its guidance, the FDA highlights three main considerations for evaluating whether deviation is necessary and for implementing protocol deviation:

1. Safety of Trial participants;
2. Compliance with good clinical practice; and
3. Minimizing risks to Trial integrity.

1. *Safety of Trial Participants*

The FDA is clear that patient safety is a top priority. Sponsors, clinical investigators and IRBs should work together to evaluate what changes might be necessary and whether the Trial should continue given the disruptions due to COVID-19. Some of the factors to be considered in determining whether the Trial should continue to include:

- The nature of the investigational product;
- The ability to monitor the safety of Trial participants while protecting participants from undue exposure to COVID-19 and complying with public health mandates;
- The impact of supply chain disruptions, both of the investigational product and of other materials such as personal protective equipment needed for Trial staff and ancillary equipment such as IV fluids, other medications and beds;
- The nature of the disease or condition under evaluation in the Trial;
- Whether modifications to the Trial protocol, such as changes to in-person visits, would be effective in monitoring safety, such as:
  - Telephone contacts;
  - Virtual visits; or

- Alternative care location visits, such as performing biospecimen collection at labs; and

- Whether other modifications to the protocol can be made that permit continuation of the Trial while addressing the above concerns.

Note that modifications that minimize or eliminate hazards related to exposure to COVID-19 and address supply chain concerns must be treated as protocol amendments and approved by the Trial sponsor and appropriate IRB, unless they are necessary to avert imminent harm, in which case they must be appropriately documented and reported. Additionally, if the determination is made to discontinue the Trial, post-Trial safety monitoring should be addressed.

2. *Compliance with Good Clinical Practice*

Mandated COVID-19 screening procedures do not need to be reported as an amendment to protocol unless the sponsor intends to incorporate the screening procedures into the data. Sponsors are encouraged to engage with IRBs as early as possible to facilitate any necessary changes to the protocol or informed consent.

In some cases, it may be possible to modify the protocol to permit shipment of investigational products to the Trial participant for self-administration. For investigational products distributed for self-administration, secure delivery methods should be used, and central and remote monitoring programs should be implemented to maintain accountability for investigational product distribution and use. However, the FDA recommends consultation with the appropriate review division before making changes to:

- Alternative sites for administration for investigational products distributed in a health care setting;
- Efficacy assessments, including changes to virtual assessments, assessment delays and alternative collection; and
- Data management and/or the statistical analysis plans.

3. *Minimizing Risks to Trial Integrity*

If policies and procedures are not already in place, the FDA recommends that sponsors, clinical investigators and IRBs address COVID-19 disruptions in policies and procedures applicable to the Trial. Additionally, the FDA notes that any policies and procedures should be "compliant with the applicable regional or national policy for management and control of COVID-19."

When changes must be made, documentation will be critical to ensuring Trial data integrity. Any alternative processes must be consistent with the protocol, including any appropriate amendments, if necessary. Any deviations that are not addressed in a protocol amendment should include documentation that explains the reasoning for the deviation. When protocol-required data is missing, the case report form should "capture *specific* information...that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information." (Emphasis in original). As noted above, changes to a Trial protocol for patient safety and well-being must still be documented. Finally, the FDA states that the clinical study report for any affected Trial must address any COVID-19 disruptions, including contingency measures, affected participants and analyses of the contingency measures implemented on the safety and efficacy of the study.

FDA ACCEPTING COMMENTS AND QUESTIONS

Due to the ongoing public health emergency, the guidance was published without initial opportunity for public comment, but the FDA is still accepting comments on the guidance here. Additionally, the FDA has provided an email address for questions on clinical trial conduct at Clinicaltrialconduct-COVID19@fda.hhs.gov.

Hall Render is tracking all FDA guidance and updates related to COVID-19.

If you have any questions on the issues discussed in or related to this post, please contact:

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