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FDA Issues Guidance On Clinical Trial Conduct During COVID-19

ALERT | March 23, 2020

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On March 18, the Food and Drug Administration (FDA) issued guidance in recognition of the extraordinary challenges that have impacted ongoing medical research in light of the coronavirus pandemic. "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic (available at: https://www.fda.gov/media/136238/download)" anticipates and addresses some of the issues facing the industry, investigators and institutional review boards.

The guidance acknowledges the disruptions posed by quarantines, site closures, travel limitations and interruptions to the supply chain for the investigational product, as well as considerations if site personnel or trial subjects become infected with COVID-19. While the declaration of a national emergency on March 13 and the subsequent impact on daily life has been profound, it is notable that a public health emergency had been declared six weeks earlier, on January 31. The strain on medical professionals and health system locations has meant investigators have already faced difficulties in meeting protocol-specified procedures and ensuring subject adherence to protocol-mandated visits. The guidance states, "FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures." In light of the evolving issues, FDA outlined general considerations to promote safety, compliance and trial integrity, while emphasizing that there can be no one-size-fits-all approach.

Notably, the guidance provides:

- **Changes permitted without institutional review board (IRB) approval:** While changes in a protocol are typically not implemented before review and approval by the IRB/independent ethics committee (IEC), urgent changes to address immediate hazards or protect the safety of research participants, such as limiting exposure to COVID-19, may be implemented without IRB approval or before filing an amendment to the investigational new drug application or investigational device exemption. These changes must be reported afterwards. Sponsors and investigators are urged to engage with IRBs/IECs as early as possible to consider these changes.

- **Mandated screening procedures need not be protocol amendments:** COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted (*e.g.*, temperature readings at point of entry) do not need to be reported as an amendment to the protocol unless the sponsor is incorporating the data collected as part of a new research objective.

- **Document the need for changes:** Any alternative process should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented.

- **Document the reason for missing data:** Acknowledging that data capture may suffer, the case report form should include specific information that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information.

- **Consult FDA on efficacy assessment issues:** For efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, and, where data is not collected, FDA expects specific documentation of the reasons for failing to obtain the efficacy assessment.

Additional considerations include:

- Keeping trial participants informed of changes to the study and to monitoring plans that could impact them.

- Evaluating alternative methods for safety assessments (*e.g.*, phone contact, virtual visit, alternative location for assessment) given that trial participants may not be able to come to the investigational site. However, any altered monitoring approach should be mindful of the ability to assure the safety of trial participants. Similarly, additional safety monitoring may be needed for trial participants who no longer have access to an investigational product or site.

- Examining alternative secure delivery methods for certain investigational products, such as those distributed for self-administration, in the event scheduled visits at clinical sites will be impacted. FDA should be consulted on plans for alternative administration for products that are normally administered in a health care setting, but that might be administered at home or elsewhere by trained but non-study personnel.

For trials where policies and procedures are not already in place, sponsors, investigators and IRBs are encouraged to establish or revise appropriate policies and procedures in anticipation of a study disruption. The guidance suggests that these changes could address issues such as the impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting and study personnel issues.

Finally, for trials impacted by the pandemic, the guidance states that sponsors should describe the impact and contingency measures in the clinical study report or a separate study-specific document. FDA will expect detail on how individual participation was altered by COVID-19, as well as analyses and corresponding discussions that address the impact of implemented contingency measures on the safety and efficacy results reported for the study.

The brief guidance signals FDA's attention to the host of complex issues emerging in real time, many of which could not have been contemplated when protocols were prepared and sites and investigators engaged. While allowing for reasonable flexibility and modification given the reality of the pandemic, the guidance underscores the continued expectation of robust efforts to maintain the safety of trial participants and the integrity of study data, with rigorous documentation. Sponsors will need to be mindful of the challenges and expectations in future preparation of their protocols and clinical trial agreements.