RESEARCH ARTICLE

Clinical Trials in the COVID-19 Era: A breakdown of FDA Guidance and Future Considerations:

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Abstract

Clinical trials that involve medical products are critical to advancing treatments in any medical field and are designed with careful thought and attention to detail. These details include careful assessment of safety parameters from patient safety visits, lab work and deliberately placed screening parameters. Meticulous planning for primary, secondary and correlative outcomes is completed by the study team and the biostatisticians involved in each study design. These precise measures are then methodically written as a clinical trial protocol and submitted to regulatory bodies such as the Food and Drug Administration (FDA) often as an Investigational Drug Application (IND) and also submitted to the Institutional Review Board (IRB) so that a study can have the appropriate regulatory approval to be tested for the desired outcome. The Principal Investigator (PI) and study team are required to follow these protocols and regulatory requirements with exactitude to maintain clinical trial integrity. While there are many models projecting variances in the timeframe of this pandemic, it is very possible that these modifications will be in place for months/years to come in varying intensities, so it is imperative that we understand them if we participate in clinical trials moving forward.

This sacred and precise structure has been reevaluated during these unprecedented times. As the tides turned in early March 2020, the United States FDA quickly realized that clinical trials and best practices needed to be addressed. Shortly after the President declared a National Emergency on March 13, 2020, the FDA released "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic." This document was then updated twice since its conception with the most recent update published on July 2, 2020. The updates have primarily been with respect to questions the agency has received since March 2020 with respect to clinical trials in the COVID-19 pandemic. This appendix contains 24 frequently asked questions and took the original 9-page guidance document to 34 pages in addressing these inquiries. The FDA guidance as a whole are nonbinding recommendations and guidance that were released with the intent to help clinical trial sites, investigatory, regulatory bodies (i.e IRB), industry partners and clinical trial consortiums that have been impacted by quarantines, site closures, travel limitations, safety for at-risk patients and many other possible challenges imposed.

Below, we highlight some of the key takeaways from the most current FDA guidance document from July 2020 to ideally help the reader translate these suggested modifications. Under references, you will find the link to this document for review in the future. Given that many of our clinical trial patients fall under the "high-risk" patient categories including those patients who are older or who have cancer or other pre-existing conditions, it is imperative that we utilize this guidance to provide the optimal care for our patients on clinical trial while ensuring their safety at the same time. This risk mitigation is the underlying theme of the released FDA guidance with considerations of alternative study conduct including:

1-Alternative Safety Assessments:

- Study visits can be conducted through alternate methods including phone contact, virtual telehealth visits, alternative locations for assessment when possible to ensure the safety of study participants.
- Obtaining informed consent for patients in isolation was also covered in the July 2020 update. This included two methods and detailed description for each on how this can be conducted through the patient signing consent and witness as appropriate.

2-Alternative Secure Delivery Methods:

- For treatments that can be self-administered off site, the FDA has allowed for delivery of drug directly to patients at home, or nursing home or to home health agency so long as existing regulatory requirements for maintaining investigational product accountability are held.
- In the July 2020 update, specific guidance on infusion delivered therapeutics were also provided. This includes the ability for investigational product (IP) to be shipped to local health care providers (HCP) for administration even if they are not listed on Statement of Investigator form (FDA 1572) as long as appropriate training and oversight can be shown.
- FDA approved IPs on unblinded studies, there is also guidance on how these may be obtained commercially should there be difficulty in obtaining from the trial site during this health emergency.

3-Alternative Monitoring Plans:

- The monitoring plan for any study, particularly for larger or later phase studies is an integral aspect to study planning. Under these FDA guidances, central or remote study monitoring should be considered over on-site monitoring to maintain oversight for clinical sites.

4-Alternative Timepoints to Correlative Analyses:

- In addition to FDA guidance, investigators may choose to make modifications to existing protocols if it is in the best interest to the patient's safety in the setting of COVID-19 and without interfering with the integrity of study data, particularly with respect to the primary outcome.

When possible, changes should be implemented after review by the IRB of record and in some cases after FDA review. If study changes lead to missing information, the FDA recommends that it is important to collect specific information on the case report forms explaining the nature of the missing data and its relationship to COVID-19. The FDA further recommends that if changes in the protocol will lead to amending the data analysis or statistical plan, the sponsor should consider consultation with the appropriate FDA review division

Based on this guidance, many other study sponsors have followed suit. This includes industry sponsors, National Cancer Institute funded studies through the National Clinical

Trials Network (NCTN) have also released guidance on how their many clinical trials are run. It is important that the investigator for any given clinical trial understand the guidelines placed not by the FDA, but also by the specific study sponsor whether (i.e. industry partner or consortium). In fact, the FDA guidance has specifically suggested that these parties of interest (sponsors, investigators, IRBs) consider establishing and implementing policies and procedures or create a revision of their current operating procedures to describe how trials will be managed and patients protected during the COVID-19 pandemic.

While many of the typically more stringent clinical trial parameters have been bent in order to maintain the safety of our study patients, it is still imperative the investigators understand their regulatory requirements. Investigators are still required to report deviations to their institutional review board (IRB) of record and provide explanation for these deviations. This could be in the form of a local or central IRB. Additionally, if there are any substantive changes in the protocol, these need to be appropriately updated to the FDA for any held investigational new drug (IND) application.

Taken together, these FDA guidelines as outlined above aim to strike a balance between risk and benefit for the patients enrolled. This balance aims to provide patients with maximal clinical benefit while still taking into account their safety as well as trial outcomes/data integrity. Beyond assuring that we have patient safety, it is also important that we are assuring the safety of the clinical and research staff involved in a particular clinical trial. This balance of patient safety, trial integrity and clinical trial outcome is what is needed to maintain clinical trials during this pandemic.

Though the United States and much of the world are very much still amidst this crisis, planning has nonetheless begun on the gradual normalization of medical treatment clinical trials. Similar to other reopening strategies nationally, this will likely be a stepwise approach in clinical trials as well. For centers who have shut down new patient enrollment during COVID-19, there will likely a gradual re-opening starting with the larger Phase2/3 consortium studies and gradually then moving to include investigator initiated Phase 2/3 studies and then to industry sponsored Phase 2/3 studies and lastly to include Early Phase/Phase 1 clinical trials as these latter tend to involve more intense safety and pharmacokinetic testing that require patients to

seek out health care providers/centers more frequently.

This pandemic has changed the way we practice medicine and has pushed us to reevaluate medical procedures, visits and testing both in and out of the clinical trial setting. In a way, there are many "silver linings" in cloud that we are currently in with the COVID-19 pandemic. In the future, we could be more open to telehealth visits, obtaining routine testing locally, shipping drug to patients, and other modifications that continue to keep patient safety at the center of the conversation in clinical trials. These allowances could encourage improved clinical trial participation and enrollment in the future, a change that is needed and welcome in the world of treatment clinical trials.

References:

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

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