FDA and EMA Guidance on Clinical Trials During COVID-19

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On March 18, the U.S. Food and Drug Administration (FDA) issued final guidance entitled, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (March 2020) (Guidance). This Guidance, issued without prior comment due to the pandemic, is for industry, investigators and IRBs. This Update includes Key Takeaways, a detailed summary of the FDA Guidance and an introduction to corresponding EMA Guidance.

Key Takeaways

– Study subject safety is paramount.

– For ongoing studies, consider suspending enrollment, continued use of the investigational product on enrolled subjects, method and timing of study subject visits, study subject withdrawal and other issues that impact subject safety.

– Protocol changes designed to "minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) do not need prior IRB approval or prior filing of an amendment to the IND or IDE, but must be reported afterwards."

– Policy and procedures may address, for example, changes to the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigators, site staff, and/or monitors due to travel restrictions, quarantine measures, resource reallocation or the COVID-19 illness itself.

– Keep study subjects informed of changes to the study and monitoring plans that could impact them.

– Consult FDA before using home nursing or other health care settings for administering investigational product, or making protocol modifications for the collection of efficacy endpoints.

– Consult FDA about amendments to the data management or statistical analysis plans.

– Before database lock, the SAP should address the handling of COVID-19-related protocol deviations.

– Document everything carefully.

– Ensure that sites properly document COVID-19-driven study changes on CRFs and other study documentation.

– Ensure that the principal investigator has a plan to manage the study if he/she or research staff become unavailable.

– Train monitors to recognize missing data and other deviations due to COVID-19.

– Be in close contact with suppliers to address potential supply chain disruption for the investigational product and other

protocol-related items.

– The EMA Guidance provides new or more detail on certain topics.

FDA Guidance

Three Goals: The Guidance is designed to assist sponsors in study subject safety, GCP compliance and trial integrity during the COVID-19 pandemic.

Challenges include quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, and infection of site personnel or trial subjects.

Control measures and next steps will depend on the nature of the disease being studied, study protocol, study design, study region and local circumstances.

A. Considerations for ongoing trials

Ensuring subject safety is paramount.

In consultation with investigators, sponsors should consider each circumstance, focus on the potential impact on study subject safety, and modify the study accordingly. Decisions may include:

– Should enrollment continue?

– For enrolled subjects, should use of the investigational product continue?

– How will study subject monitoring change?

– Should study assessments be delayed?

– Should subjects be withdrawn from the study?

Inform subjects: FDA notes that it is "critical" to keep study subjects informed of changes to the study and monitoring plans that could impact them.

Consider making subject study visits off-site/virtual: Are alternative methods for study subject safety assessments feasible (e.g. phone contact, virtual visit, local labs/imaging centers)? Is an in-person visit necessary to assure full safety (e.g. to conduct a procedure needed to assess safety or safe use of the product)? This analysis impacts whether to discontinue use or administration of the investigational product.

Additional safety monitoring may be needed for subjects who no longer have access to the investigational product or study site.

COVID-19 screening procedures:

Screening procedures mandated by the site do not need to be reported as a protocol amendment, even if done during study visits, unless the sponsor will use the data from the screening as a new objective.

Protocol changes:

Certain protocol changes do not need prior IRB approval or FDA filing: Protocol changes are usually implemented after review and approval by the IRB and sometimes by FDA. Here, FDA is encouraging sponsors and investigators to engage with the IRB as soon as possible when "urgent or emergent" changes to the protocol or informed consent are anticipated due to COVID-19. Protocol changes designed to "minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) do not need prior IRB approval or prior filing of an amendment to the IND or IDE, but must be reported afterwards." See 21 CFR 56.108(a)(4), 21 CFR 56.104(c), 21 CFR 312.30(b)(2)(ii), and 21 CFR 812.35(a)(2). Sponsors and investigators should work with their IRBs to prospectively define procedures to prioritize the reporting of deviations that may impact subject safety.

Document study changes: Sponsors and investigators should document the reason for process changes, how COVID-19-related restrictions led to study conduct changes, the duration of the changes, which subjects were impacted and for how long.

Missing information due to changes in study visit schedules, missed visits or patient discontinuation:

Case report forms should capture specific information that explains why the data is missing, including the relationship to COVID-19. Summarize this in the clinical study report.

Investigational product administration – alternatives:

For self-administered products normally provided at study visits, alterative secure delivery methods may be considered. If the investigational product needs to be administered in a health care setting, FDA recommends consulting the FDA review division on plans for alternative administration, if feasible (e.g. home nursing or other sites by trained non-study personnel).

Efficacy assessment changes to protocol – consult with FDA:

FDA recommends consulting with the FDA review division about protocol modifications for the collection of efficacy endpoints (e.g. virtual assessments, assessment delays, alternative collection of specimens). Where efficacy endpoints are not collected, document the reasons, including the specific limitation imposed by COVID-19.

Data management and/or statistical analysis plans (SAP) impact:

If protocol changes will lead to amending either plan, the sponsor should consult with the FDA review division. Before database lock, the sponsor should address in the SAP how COVID-19-related protocol deviations will be handled.

Site monitoring:

If on-site monitoring is not possible, sponsors should consider using central and remote monitoring.

B. In general, and if policies and procedures are not already in place for applicable trials

Sponsors, investigators and IRBs should establish or revise existing policy and procedures to describe how study subjects will be protected and to manage study conduct during possible study disruption due to COVID-19. These should comply with regional and national policy for COVID-19. A protocol amendment may be required. Changes could address, among other things, the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigators, site staff and/or monitors due to travel restrictions, quarantine measures or the COVID-19 illness itself.

C. For all trials that are impacted by the COVID-19 pandemic

Sponsors should document in the clinical study report or a separate study-specific document:

– Contingency measures implemented to manage study conduct disruptions due to COVID-19.

– A list of all subjects affected (by COVID-19-related study disruption) by unique subject number identifier and site and a description of how the subject's participation was altered.

– Analysis and discussion of impact of the study changes (e.g. discontinuation from investigational product or study; changes to crucial safety or efficacy data collection) on the safety and efficacy results.

EMA Guidance

On March 20, the European Commission, Head of Medicines Agency, and European Medicines Agency (EMA) published Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (Version 1 (20/03/2020)) (EMA Guidance). The EMA Guidance was issued without prior public consultation and will likely be updated.

While the EMA Guidance covers similar ground as the FDA Guidance, the EMA Guidance provides new or more detail on certain topics such as:

– Transferring subjects to a new trial site

– Principal investigator unavailability

– Reconsenting subjects

– Changes to distribution of the investigational product

– Reimbursement of exceptional travel expenses

– Changes to monitoring (Member States do not permit remote source data verification)

– New studies to treat COVID-19.

The EMA Guidance also reminds sponsors and investigators to comply with Member State legislation and guidance, which may complement or, in some cases, take priority over the EMA Guidance.

Access the FDA Guidance.

Access the EMA Guidance.

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

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