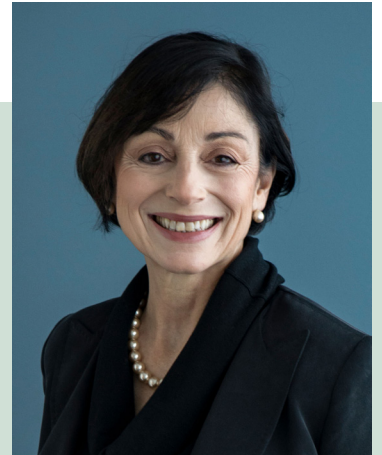


Potential Consequences of SARS-CoV-2 to Ongoing Clinical Programs: The FDA Perspective

“This disruption impacts all facets of the drug development process, from the Sponsor company, to the supply chain of investigational treatments to the productivity of study sites.”



The virus SARS-CoV-2 and the resulting COVID-19 disease have created devastating impacts around the globe on lives and livelihood, including major disruption of ongoing research and development activities for innovative therapies. From many perspectives the spread of SARS-CoV-2 has impacted and will continue to impact ongoing global registrational programs for a variety of disorders especially those not directly addressing the treatment or prevention of the SARS-CoV-2.

This disruption impacts all facets of the drug development process, from the Sponsor company, to the supply chain of investigational treatments to the productivity of study sites. The FDA has issued guidance to address the challenges that may arise from a range of disruptions that could impact the validity and integrity of clinical programs.

The FDA has noted that the spread of the virus may lead to GCP violations and protocol deviations, including impact on trial endpoints and safety collection. FDA’s Center for Drug Evaluation and Research Director Janet Woodcock stated that “trials may be able to shift to tele-outcome assessments”, but others “may be damaged and may have to halt and not start up again until we can interact more freely”.

FDA’s recent guidance, “Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic” addresses the potential impacts to ongoing trials. The guidance provides stakeholders in the drug development and approval process with critical considerations for ongoing trials.

Potential COVID-19 impacts

Trials may be impacted in a variety of ways. Some sites have had to close down or have witnessed significant recruitment delays due to the inability of patient travel, illness, or redeployment of study personnel to address COVID-19 patients or trials. These limitations can greatly impact study continuity and procedures to maintain study integrity. In making decisions on trial continuity, Sponsors will need to do a robust assessment of trial conduct that may impact patient safety, GCP, drug storage and administration, and protocol procedures.

Safety first

All ongoing clinical programs impacted by COVID-19 will require a full gap analysis to understand how the pandemic impacts the safety and well-being of trial subjects at the site level. This may ultimately result in a number of clinical protocol changes, including updates to the informed consent. How these study participants should be managed will greatly depend on the disease being studied, availability of study drug and/or alternatives, potential impact of the virus on study subjects and site personnel, and the ability to continually monitor the safety of study subjects. It is recommended that Sponsors inform the IRB / IEC and clinical investigators on any protocol implications and amend accordingly.

Alternative remote monitoring approaches should be considered. Monitoring methods other than site visits may include phone contact, remote visits, and other local data collection. In addition, patient safety resulting from direct COVID-19 infection must be taken into consideration. COVID-19 screening procedures may be mandated by local healthcare systems and must be followed. FDA has indicated that these local screening procedures do not need to be reported as a protocol

amendment even if performed during clinical study visits (unless this data is being collected as part of a new study program).

Study integrity: Document, document, document

Probably the most difficult and challenging aspect related to the impact of SARS-CoV-2 is how to salvage ongoing trials that support registration. The FDA acknowledges that protocol violations are likely to be unavoidable. Nonetheless, Sponsors must anticipate these violations to the best of their abilities and take steps to address those violations that are likely to occur. Here are some components mentioned in FDA's guidance document:

A) Protocol deviations

In most cases, protocol violations will occur as a result of alternative procedures that are implemented. It is important that all alternative procedures are fully documented, including the reasons for the alternative methods. Sponsors will need to document the information that may be missing due to missed visits, changes to monitoring timing, or other reasons for discontinuation. In addition thought must be given to study drug accountability and if administration of investigational agents can continue at home. Drug supply and storage methods will need to be documented and recorded. For more advanced technologies, it is possible that delivery may occur by other specialized personnel. However, this may prove to be a challenge as special storage conditions may not be possible.

B) Study endpoints/and statistical plans

Clinical endpoints in an ongoing study that cannot be directly measured due to site visit constraints are likely to be negatively impacted. Sponsors are being asked to consult with their respective review divisions to obtain feedback on any proposed changes to

endpoint assessments, whether due to delays, inability to obtain protocol defined measurements, or because they have implemented alternative measures, The reasons for these changes would need to be fully documented including the reasons the original endpoint could not be obtained as a result of the pandemic . Finally, it will be critical to obtain respective FDA review division agreement prior to database lock and describe how these deviations to endpoint collection will be impacted and managed in the updated statistical analysis plan.

C) Documentation in study reports

In all of these cases, documentation and a full explanation of how the study was impacted will need to be addressed in the final study reports. The FDA requires a detailed list of protocol deviations with explanations for each trial participant, and study site. Alternative measures implemented to manage study conduct, changes to analyses and study procedures, including timing, monitoring, and impact on safety and efficacy assessments need to be included.

Trial salvage

The FDA is updating the guidance as information evolves regarding the impact of the pandemic on registrational programs. Certainly, each situation and protocol is unique based on the disease under study, seriousness of patient population, and study goals. However, all stakeholders, including Sponsors, investigators, IRBs and FDA, must follow a robust ap-

proach to documentation and communication in order to ensure safety of study participants.

While many trials may be halted or paused due to SARS-CoV-2, there is critical data already gathered. Trial integrity is of the utmost importance to support novel therapies for diseases with unmet needs. Rescue of registrational trial information is critical to support the benefit/risk evidence needed to support investigational program continuity and eventual approval once programs can be resumed.

Other Resources

Contact information for Review Divisions:

CDER: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs>

CBER: <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/contactscenter-biologics-evaluation-research-cber#indcont>

CDRH: <https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization>

References

Pink Sheet March 31, 2020: CDER's Woodcock On COVID-19: Missed User Fees Unlikely, But Some Work Will Be 'Set Aside'

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID 19 Pandemic (initially published March 2020)

About the author

Dr Laurie Smaldone Alsup has led multinational teams in over 100 US FDA and EMA/ national proceedings, including FDA milestone meetings, Advisory Committee hearings and EU Scientific Advice and Oral Explanations. She is a recognized global leader in the biopharmaceutical sector for successful product development and regulatory solutions for serious and rare disorders.

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