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COVID-19 and Clinical Trials: Considerations for Sites and Investigators

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March 31, 2020

Healthcare providers and institutions are on the front lines in the battle against the novel coronavirus (COVID-19), but the impacts of this public health crisis extend well beyond emergency patient care. As the pandemic progresses, many clinical trials will be postponed or canceled as a result of patient safety concerns, community health requirements, travel restrictions, a lack of resources, redeployment of staff, and disruptions to supply chains (including investigational products). As oversight authorities and sponsors work quickly to publish guidance regarding the immediate impacts to clinical trials, clinical trial sites and investigators should implement plans to assess the viability of ongoing and upcoming trials, implement and document necessary trial changes, and communicate with participants and sponsors.

Determine Which Trials Will Continue

Complex overlapping issues will impact the viability of many trials. Some trials might continue during the pandemic while others may not, depending on trial-specific risks and benefits to participants and staff, local community public health guidelines, site resources, trial design, sponsor capabilities and preferences, and protocol requirements. At present, there is no consensus regarding which trials should continue during the pandemic (other than COVID-19 research). However, several government agencies and accreditation organizations have communicated recommendations and interim policies to describe their positions and response strategies. On March 16, 2020, the National Institutes of Health (NIH) published "Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected by COVID-19."[i] On March 18, 2020, the Food and Drug Administration (FDA) published a final version of nonbinding guidance titled "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" for sponsors, investigators, and Institutional Review Boards (IRBs),[ii] and on March 27, 2020, the FDA updated that guidance with FAQs.[iii] On March 20, 2020 the Association for the Accreditation of Human Research Protection Programs (AAHRPP) published "Guidance on HRPP Response to COVID-19" for those involved in human subjects research protection programs.[iv] On the same day, the European Commission published "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic."[v]

While all of these organizations stressed the significance of protecting the safety of participants, none provided an explicit framework for deciding which trials may or should continue during the pandemic. As individual sites and investigators comprehensively analyze whether to continue a particular trial, they might consider how other sites have established criteria for that decision.[vi] While the FDA and AAHRPP both noted that ensuring the safety of trial participants is "paramount," if sites and investigators will continue with some trials, they should immediately prepare to implement appropriate changes.

Implement and Document Appropriate Changes for Continuing Trials

To enact appropriate changes, it may be necessary to develop new processes, deviate from existing trial protocols, and revise or draft institutional policies to safely and effectively proceed with clinical trials. The primary goal of implementing such changes should be to ensure the safety of participants, trial personnel, and the community.[vii] However, sites and investigators should also consider whether the changes will allow them to maintain good clinical practice (GCP) compliance and protect trial integrity.[viii]

Sites and investigators should also take into account that the reviewing IRB must review changes to the protocol. Although IRBs typically review and approve trial protocol changes before they are implemented, there may be compelling reasons to immediately implement some changes "to eliminate apparent immediate hazards" to participants.[ix] Fortunately, AAHRPP and some IRBs have indicated that there will be increased cooperation and flexibility in processing requests for changes and reviewing changes already implemented. Not all changes require a formal amendment to the trial protocol.[x]

Sites and investigators should not forget to document trial changes appropriately. The FDA noted that investigators should be prepared to document "how restrictions related to COVID-19 led to the changes in study conduct and [the] duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted."[xi] Sites and investigators should also plan to keep a record of all participants affected by COVID-19 in the trial "by unique subject number identifier," as well as document how the individual's participation in the trial changed as a result of COVID-19.[xii] In addition, if the impact of COVID-19 results in "missing protocol-specific information" from trial records, "*specific"* information should be captured in the case report form and summarized in the trial report to explain the reason for the missing information.[xiii] The FDA also recommends that sites and investigators (and sponsors and IRBs) establish new or amend existing policies and procedures to address changes due to COVID-19.[xiv]

Communicate Trial Changes

As the COVID-19 crises evolves, sites and investigators should immediately and regularly communicate with trial sponsors. It is also important that sites and investigators communicate with trial participants to convey

information about changes to the trial. The AAHRPP suggests that IRBs should be "flexible in [reviewing] how researchers notify participants of changes to research."[xv]

Conclusion

Most areas of daily life have been significantly impacted by the COVID-19 pandemic, and this includes the conduct of clinical trials. To protect the health and safety of trial participants, staff, and the community, sites and investigators must be simultaneously rigorous and flexible. Sites and investigators should develop criteria for determining whether or not to proceed with a current or proposed study, vet changes through the appropriate bodies, document policies and process changes, and communicate changes with sponsors and participants.

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Endnotes

[i] NATIONAL INSTITUTES OF HEALTH, *Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected by COVID-19,* Notice Number: NOT-OD-20-087 (March 16, 2020), https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-087.html.

[ii] FOOD AND DRUG ADMINISTRATION, *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards* (March 2020), https://www.fda.gov/media/136238/download.

[iii] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic.

[iv] ASSOCIATION FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS, *Guidance on HRPP Response to COVID-19* (March 20, 2020), https://admin.aahrpp.org/Website%20Documents/Guidance%20for%20Accredited%20Organizations%20on%20COVID-19%20(2020-03-23)%20(for%20distribution).pdf.

[v] EUROPEAN COMMISSION, *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic*, Version 1 (March 20, 2020), https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

[vi] See JOHNS HOPKINS MEDICINE, *Essential Information for Human Subjects Research Teams Related to COVID-19,* https://www.hopkinsmedicine.org/institutional_review_board/news/covid19_information.html/index.html (last visited March 25, 2020); see also UNIVERSITY OF CALIFORNIA SAN FRANCISCO, OFFICE OF RESEARCH, *Revised Interim UCSF Policy on Human Subjects-Related Research Visits at San Francisco Campuses during COVID-19 Outbreak,* (effective March 16, 2020), https://research.ucsf.edu/revised-interim-ucsf-policy-human-subjects-related-research; and see also COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK, *COVID-19 (Novel Coronavirus): Frequently Asked Questions Relating to Research*, https://research.columbia.edu/covid-19-novel-coronavirus-frequently-asked-questions-relating-research (last visited March 25, 2020).

[vii] Appropriate changes might include:

- assessing participant safety through "alternative methods" (e.g., phone visits, video visits, alternative physical locations, etc.);
- discontinuing administration of investigational product (due to supply problems, safety risks, and monitoring capabilities, etc.);
- delaying enrollment or site activation;
- extending the trial;
- transferring participants to other trial sites;
- utilizing alternative providers or facilities for imaging, laboratory services, home visits, or physical exams;
- reducing the number of face-to-face trial visits, increasing the scheduled time between visits, or eliminating some visits;
- shipping investigational products directly to participants;
- conducting remote or virtual study monitoring; and
- conducting remote or virtual site initiation visits (SIVs), or delaying SIVs.

[viii] FOOD AND DRUG ADMINISTRATION, *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards* at page 4 (March 2020), https://www.fda.gov/media/136238/download.

[ix] See 21 CFR 56.108(a)(4); see 45 CFR 46.108(3)(iii); see also ASSOCIATION FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS, *Guidance on HRPP Response to COVID-19* (March 20, 2020), https://admin.aahrpp.org/Website%20Documents/Guidance%20for%20Accredited%20Organizations%20on%20COVID-19%20(2020-03-23)%20(for%20distribution).pdf.

[x] ADVARRA, *Coronavirus Guidance: Answers to Your Urgent Questions About the Research Impact of COVID-19,* https://www.advarra.com/coronavirus-guidance/#changes-to-protocol (last visited March 26, 2020); WIRB-Copernicus Group, News Center, *Changes to Research Made in Response to COVID-19,* https://www.wcgclinical.com/changes-to-research-made-in-response-to-covid-19/ (last visited March 25, 2020).

[xi] FOOD AND DRUG ADMINISTRATION, *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards* at page 7 (March 2020), https://www.fda.gov/media/136238/download.

[xii] *ID*.

[xiii] *ID*.

[xiv] *ID* (concluding that policies and procedures "could address, but [should] not be limited to, the impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself").

[xv] ASSOCIATION FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS, *Guidance on HRPP Response to COVID-19* (March 20, 2020), https://admin.aahrpp.org/Website%20Documents/Guidance%20for%20Accredited%20Organizations%20on%20COVID-19%20(2020-03-23)%20(for%20distribution).pdf.