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FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

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Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on April 16, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or the Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1106 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and the FDA webpage titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an e-mail request to Clinicaltrialconduct-COVID19@fda.hhs.gov to receive a copy of the guidance. Please include the document number FDA-2020-D-1106 and complete title of the guidance in the request.

Questions

For questions about this document, contact us via email at Clinicaltrialconduct-COVID19@fda.hhs.gov

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I. Introduction

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from threats including emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support continuity and response efforts to this pandemic.

FDA is issuing this guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 public health emergency. The appendix to this guidance further explains those general considerations by providing answers to questions that the Agency has received about conducting clinical trials during the COVID-19 public health emergency.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service (PHS) Act.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR

10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2]

FDA recognizes that the COVID-19 public health emergency may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product,[3] or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. 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 public health control measures. Although the necessity for, and impact of, COVID-19 public health control measures on trials will vary depending on many factors, including the nature of disease under study, the trial design, and in what region(s) the study is being conducted, FDA outlines the following general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity. The appendix further explains those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 public health emergency.

[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx).
[2] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.
[3] For the purposes of this guidance, the term *investigational product* refers to human drugs and biological products, and medical devices.

III. Discussion

A. Considerations for ongoing trials:

- Ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Study decisions may include those regarding continuing trial recruitment, continuing use of the investigational product for patients already participating in the trial, and the need to change patient monitoring during the trial. In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them.

- Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), may determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial.

- Since trial participants may not be able to come to the investigational site for protocol-specified visits, sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible, and would be sufficient to assure the safety of trial participants. Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants (for example to carry out procedures necessary to assess safety or the safe use of the investigational product appropriately); in making the decision to continue use or administration of the investigational product, the sponsor should consider whether the safety of trial participants can be assured with the implementation of the altered monitoring approach.

- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

- The need to put new processes in place or to modify existing processes will vary by the protocol and local situation. For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants.

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.

- Changes in a protocol are typically not implemented before review and approval by the IRB/IEC, and in some cases, by FDA. Sponsors and clinical investigators are encouraged to engage with IRBs/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Such changes to the protocol or investigational plan 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) may be implemented without IRB approval or before filing an amendment to the investigational new drug (IND) or investigational device exemption (IDE), but are required to be reported afterwards.[4] FDA encourages sponsors and investigators to work with their IRBs to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants.

- The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted.

- Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). It will be important to capture *specific* information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.

- If scheduled visits at clinical sites will be significantly impacted, certain investigational products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods. For other investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

- With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).

[4] See 21 CFR 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), and 812.35(a)(2).

- If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses.

- If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites.

B. In general, and if policies and procedures <u>are not already in place</u> for applicable trials:

- Sponsors, clinical investigators, and IRBs should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites. Changes to policy and procedures could address, but not be limited to, 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. Policy and procedures should be compliant with applicable (regional or national) policy for the management and control of COVID-19. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations.[5]

C. For all trials that are impacted by the COVID-19 public health emergency:

Sponsors should describe in appropriate sections of the clinical study report (or in a separate study-specific document):

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
2. A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.
3. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Robust efforts by sponsors, investigators, and IRBs/IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. As stated above, FDA recognizes that protocol modifications may be required, including unavoidable protocol deviations

[5] See 21 CFR 312.30(b), and 812.35(a). Under applicable federal regulations, investigators must engage with the Drug Enforcement Administration when seeking to amend protocols for research involving Schedule I substances under the Controlled Substances Act by requesting a modification of the approved protocol. See 21 CFR 1301.18.

due to COVID-19 illness and/or COVID-19 control measures. Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, will be important.

IV. Additional Resources

For further questions on clinical trial conduct during the COVID-19 public health emergency, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

Contact information for FDA's review divisions is as follows:

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/contacts-center-biologics-evaluation-research-cber#indcont

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

Appendix: Questions and Answers

Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 public health emergency?

Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), should assess whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial. As part of this assessment, sponsors should carefully consider the following aspects of clinical trial conduct when deciding how or whether to proceed with a clinical trial:

- Assessing whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.
- Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial and properly assess and manage safety issues that may emerge.
- Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?
- Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified in-person assessments can instead be conducted virtually.
- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the treatment schedule is revised, or if the clinical site is unable to properly store the product for the needed duration.
- Assessing the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial. Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize any potential disruptions?
- Assessing whether there will be continued operations of, and adequate communications with, IRB/IEC and Data Monitoring Committee (DMC) staff, if applicable, to support trial needs.
- Assessing whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal and State authorities to control the virus.

Involvement of a study's DMC, if one has been established, can provide support for the assessments

discussed above. Since a primary responsibility of the DMC is assuring the safety of participating trial participants, the DMC's assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider.

The risks and benefits of continuing a trial are likely different than a decision to initiate a trial (other than trials intended to evaluate investigational treatments or vaccines for COVID-19). Given the evolving situation, with likely increasing impacts on investigators, staff, and supply chains, sponsors should carefully consider the ability to effectively mitigate risks such that patient safety and trial integrity are assured. In addition, it is important to consider whether initiation of the trial could interfere with public health measures implemented by Federal and State authorities to control the virus.

Q2. What key factors should sponsors consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to the trial participant during the COVID-19 public health emergency?

There may be circumstances in which an investigational product (either a drug, biological product, or medical device) appears to be providing benefit to the trial participant. A sponsor deciding whether to continue administering or using such a product during the COVID-19 public health emergency should carefully consider context-dependent issues, including whether a trial participant appears to be benefitting from treatment with the investigational product, whether there are reasonable alternative treatments, the seriousness of the disease or condition being treated, and the risks involved in switching to an alternative treatment if necessary. FDA recognizes that in some circumstances it may be necessary (e.g., based on lack of product supply or inability to administer or ensure the safe use of the investigational product) to discontinue investigational product administration in a trial. If there are individual trial participants for whom discontinuing the investigational product might present a substantial risk (e.g., trial participants perceived by the investigator as having a clinical benefit from the investigational product), the sponsor should consider amending the protocol, after discussion with the relevant review division, to limit investigational product use to those patients with apparent benefit and discontinue investigational product use to other participants. In all cases, if a trial participant is discontinued from an investigational therapy, it is important that there be appropriate management after discontinuation.

Q3. How should sponsors manage protocol deviations and amendments to ongoing trials during the COVID-19 public health emergency?

FDA recognizes that during the COVID-19 public health emergency, sponsors of clinical trials may need to modify protocol-specified procedures. As is discussed in the main body of this guidance, for protocol deviations necessitated by the impact of the current COVID-19 public health emergency, the sponsor should document the specific protocol deviation and the reason for the deviation. The sponsor can document protocol deviations using its standard processes, or given the larger expected number of such deviations, use alternative documentation approaches. For example, if visits are to be conducted by telephone/video contact rather than at the investigational site as specified in the protocol, documentation that provides a listing of all study visits that are deviations from the protocol due to the current COVID-19 situation (i.e., study reference number, patient ID, date of visit) generally would be acceptable.

For a study-wide change in protocol conduct, protocol amendments that are necessary to prevent

imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the IRB/IEC and notification to FDA through filing a protocol amendment to the investigational new drug (IND) or deviation from the investigational device exemption (IDE).[1]

For studies under an IND, 21 CFR § 312.30(b) specifies that sponsors need to submit a protocol amendment describing any change in a phase 1 protocol that *significantly affects* the safety of subjects, or any change in a phase 2 and 3 protocol that *significantly affects* the safety of subjects, the scope of the investigation, or the scientific quality of the study. Pausing enrollment in a trial to decrease potential exposure to COVID-19 would not generally be expected to significantly affect subject safety, the scope of the investigation, or the scientific quality of the study; therefore, submitting a protocol amendment would not be required under the regulation for such a pause.

Protocol amendments that are not required to prevent imminent safety risks to patients can be implemented once they are submitted to FDA and IRB approval has occurred.[2] FDA recognizes that during the rapidly evolving circumstances of a pandemic, a sequence of changes may be needed to address those circumstances. Consolidating several protocol modifications in a single protocol amendment would be acceptable but should be done expeditiously. Clinical investigators must document as protocol deviations any modifications to protocol-specified procedures that occur prior to IRB approval and FDA submission of the protocol amendment implementing the modification.[3]

For studies under an IDE, 21 CFR 812.35(a) generally requires prior FDA approval before implementing changes to the investigational plan. However, under 21 CFR 812.35(a)(3), changes to the protocol that, based on credible information, the sponsor determines do not affect the validity of the results from the study; the likely patient risk to benefit relationship; the scientific soundness of the investigational plan; or the rights, safety or welfare of the subjects may be made without prior FDA approval, if the sponsor reports the modifications to the agency within 5 days of implementing the changes. Because of the unique and evolving circumstances surrounding the impact of COVID-19, we understand that it may be challenging to submit 5-day Notices within the required timeframe. Sponsors may consolidate implemented changes when submitting 5-day Notices and should update the IDE as soon as possible.

Q4. How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 public health emergency?

For **IND studies**, the sponsor should submit a formal amendment to its IND, with the following information added to the cover letter in the subject line:

PROTOCOL AMENDMENT – COVID-19

TITLE OF PROTOCOL

Sponsors should summarize the major changes made to the protocol related to COVID-19 in the cover letter and should include a tracked changes version of the protocol to facilitate review. As with other protocol amendments, sponsors may implement protocol amendments due to COVID-19 upon

[1] See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).
[2] See 21 CFR 312.30(b)(2).
[3] See 21 CFR 312.62.

submission to FDA if approved by the IRB. Sponsors seeking FDA input prior to implementation should indicate that in the cover letter.

For IDE studies, the sponsor should submit a supplement to its existing IDE, with the following information added to the cover letter in the subject line:

CHANGE IN PROTOCOL SUPPLEMENT – COVID-19 or
NOTICE OF IDE CHANGE – COVID-19, as applicable

TITLE OF PROTOCOL

The submission to the IDE should contain a tracked changes version of the protocol to facilitate review.

Q5. Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of the trial participant and it will not impact data integrity?

FDA regulations allow for changes to be made to the investigational plan or protocol without prior FDA review or approval, if the change is intended to eliminate an apparent immediate hazard or to protect the life and well-being of subjects.[4] Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to FDA. Since this reflects a protocol deviation (until the amendment is approved), documentation of the required deviations, as described above, would generally be acceptable (i.e., a document that lists each deviation, study reference ID, patient ID, and date). For example, documenting that all protocol-specified visits will be done by telephone contact rather than on-site visits, and that procedures requiring in-person visits will either not be conducted, or performed by other means (specified, as appropriate). Since the change to telephone or video contact visits would likely result in some protocol-required procedures not being conducted (e.g., vital signs, blood samples for safety laboratory studies), the sponsor must evaluate the potential impact on patient safety, and consider how to mitigate risks to patients, including the need to discontinue the investigational product.

For IDE studies, sponsors are required to report deviations implemented to address the imminent safety risk to FDA within 5 working days after learning of the deviations. We recognize that challenges related to the COVID-19 pandemic may make it difficult to meet this timeframe. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. With the rapid changes in clinical trial conduct that may occur due to the COVID-19 public health emergency, including multiple deviations to address patient safety, what is the best way for sponsors and investigators to capture these data?

As noted in the main body of this guidance, it is important to capture *specific* information for individual participants that explains the basis for missing protocol-specified information that includes

[4] See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).

the relationship to COVID-19 (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA. If it is not possible to capture this information in the case report form(s), sponsors may develop processes that enable systematic capture of these data across the sites in a manner that enables the appropriate analysis when the data are submitted to FDA. Sponsors may also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations.

Q7. If patients are currently dispensed investigational product through a pharmacy at the clinical trial site for self-administration at home, can a sponsor switch that to home delivery without amending the protocol?

If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational product accountability remain; these requirements must be addressed and documented.[5] If the protocol indicates pharmacy dispensing for self-administration at home, and this is changed to direct-to-patient shipments, then a protocol amendment would be required to permit home delivery of investigational product.[6] If the extent of home delivery is limited to certain participants and not the entire population described in the protocol, documenting the change in the mechanisms of distribution of investigational product administration through protocol deviations may also be acceptable. If the change in the mechanisms of investigational product distribution is then included in a protocol amendment, such a change may be part of a "cumulative" amendment that includes a number of changes that accrue, rather than an urgent protocol change.[7]

Q8. If patients are currently receiving an investigational product infusion at the clinical trial site, can a sponsor switch to home infusion?

Sponsors should consider the safety risk to trial participants who would miss an investigational product infusion because of the inability to come to the clinical trial site. In general, for investigational product that is usually administered in a health care setting, consulting the appropriate FDA review divisions is recommended regarding plans for alternative sites for administration (e.g., home nursing or alternative sites by trained but non-study personnel). For example, consulting FDA would be strongly advised for complex investigational products (e.g., cellular therapy and gene therapy products) where potentially altered storage and handling conditions could adversely affect product stability. In all cases, applicable requirements for maintaining required investigational product storage conditions (prior and after reconstitution), investigational product reconstitution specifications per the Investigator's Brochure, and investigational product accountability remain and must be addressed and documented. Storage conditions and investigational product accountability should be considered if the protocol is amended to permit alternative site infusions. Defining circumstances when discontinuing investigational product administration, while continuing study participation albeit with potentially delayed assessments, may be an appropriate option when suitable alternative arrangements cannot be made.

[5] See 21 CFR 312.60, 312.62, and 812.140.
[6] See 21 CFR 312.30(b), and 812.35(a).
[7] See 21 CFR 312.30(b), 812.35(a), and 812.150(a)(4).

Q9. Considering that there likely will be delays to on-site monitoring of clinical trials during the COVID-19 public health emergency, what are FDA's expectations in such circumstances?

FDA recognizes that monitors may not be able to access the trial sites for on-site visits in a timely manner during the COVID-19 public health emergency. Sponsors should work to find alternative approaches to maintain trial participant safety and trial data quality and integrity, such as enhanced central monitoring, telephone contact with the sites to review study procedures, trial participant status, and study progress, or remote monitoring of individual enrolled trial participants, where appropriate and feasible. FDA recognizes that delays in on-site monitoring may result in delayed identification of GCP non-compliance (including major protocol deviations) at the clinical trial site(s) (including protocol deviations not due to the impact of COVID-19). Sponsors should carefully document situations where monitors were unable to access, or had to delay monitoring of, a clinical site. Sponsors/monitors should also include in their documentation of protocol deviations or other GCP non-compliance issues identified at clinical sites whether delayed identification was due to postponed monitoring. FDA recognizes that unique situations at clinical sites will occur due to COVID-19 control measures and will consider these circumstances when evaluating inspectional observations.

Q10. How do I obtain signed informed consent from a patient who is in isolation when a COVID-19 infection control policy prevents us from entering the patient's room to collect a signed informed consent form?

FDA regulations generally require that the informed consent of a trial participant be documented by the use of a written consent form that has been approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent (21 CFR 50.27(a)). In light of COVID-19 infection control measures, the following procedure would satisfy documentation of this requirement if the patient signing the informed consent is in COVID-19 isolation.[8]

- If the technology is available, electronic methods of obtaining informed consent should be considered.[9]
- When it is not possible to obtain informed consent electronically, the sponsor should consider taking the following steps:
  1. An unsigned consent form is provided to the patient by a heath care worker who has entered the room
  2. If direct communication with the patient in isolation is not feasible or safe, the investigator (or their designee) obtains the patient's phone number and arranges a three-way call or video conference with the patient, an impartial witness and, if desired and feasible, additional participants requested by the patient (e.g., next of kin)
  3. To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
     - Identification of who is on the call

[8] The procedures suggested do not apply to the exception from general informed consent requirements under 21 CFR 50.23 or the exception from informed consent requirements for emergency research under 21 CFR 50.24.

[9] See guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent In Clinical Investigations* (December 2016), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers.

- Review of the informed consent with the patient by the investigator (or their designee) and response to any questions the patient may have
- Confirmation by the witness that the patient's questions have been answered
- Confirmation by the investigator that the patient is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone
- Verbal confirmation by the patient that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession

If the signed informed consent document cannot be collected from the patient's location and included in the study records, FDA considers the following two options acceptable to provide documentation that the patient signed the informed consent document:

- A dated attestation by the witness who participated in the call and by the investigator that the patient confirmed that they agreed to participate in the study and signed the informed consent.

  OR
- A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient.

A copy of the informed consent document signed by the investigator and witness should be placed in the patient's trial source documents, with a notation by the investigator of how the consent was obtained (e.g., telephone call). The trial record at the investigational site should document how it was confirmed that the patient signed the consent form (i.e., either using attestation by the witness and investigator or the photograph of the signed consent). The note should include a statement of why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

If the patient is unable to provide informed consent and there is a legally authorized representative, investigators must obtain written consent from the participant's legally authorized representative in accordance with 21 CFR 50.27(a).

Q11. How do I obtain informed consent from a patient unable to travel to a clinical trial site where electronic informed consent is not an option?

Investigators may also need to obtain informed consent from a potential trial participant or their legally authorized representative when these individuals are unable to travel to the site where the investigator is located due to COVID-19 illness or travel restrictions. When investigators do not have electronic informed consent (eIC) capabilities,[10] methods of obtaining informed consent other than a face-to-face consent interview may still be acceptable if those methods allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enroll as a subject in the clinical investigation or is the legally authorized representative of the subject. For example, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's legally authorized representative can read the consent form during the discussion. After the consent discussion, the subject or the subject's

[10] Id.

legally authorized representative can sign and date the consent form. Options for returning the document to the clinical investigator may include facsimile, scanning the consent form and returning it through a secure e-mail account, or posting it to a secure internet address. Alternatively, the subject may bring the signed and dated consent form to his/her next visit to the clinical site, if restrictions on traveling to the clinical trial site are alleviated, or mail it to the clinical investigator. The case history for each subject must document that informed consent was obtained prior to participation in the trial.[11] In addition, the person signing the consent form must receive a copy of the consent form.[12] Although FDA regulations do not require the subject's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.

If concerns exist about having subjects mail to the investigator potentially contaminated consent documents from the subject's location, the investigator may employ the procedures described above for enrolling patients in isolation through the use of a photographic image of the signed consent form transmitted through electronic means.

The subject or the subject's legally authorized representative must sign and date the informed consent form before the investigator may conduct any study-related procedures involving the subject.[13] Where it is not feasible for investigators to receive the signed consent form prior to beginning study-related procedures, the investigators should have the subject or legally authorized representative confirm verbally during the consent interview that the subject or legally authorized representative has signed and dated the form. In addition, the overseeing IRB must review and approve the planned informed consent process.[14]

Q12. What factors should sponsors consider when deciding whether to implement remote performance outcome (PerfO) assessments or interview-based clinician-reported outcome (ClinRO) assessments during the COVID-19 public health emergency?

ClinROs and PerfOs are two types of clinical outcome assessments used in some clinical investigations. For purposes of this guidance, a ClinRO is a measurement by a trained health care professional after observing a subject's health condition, and a PerfO is a measurement based on a standardized task performed by a subject that is administered and evaluated by an appropriately trained individual or is individually completed.[15]

Although remote administration of interview-based ClinRO assessments and PerfO assessments may be feasible depending on the context of use (e.g., methodology of the assessment and subject safety considerations), not all assessments can be done remotely. Sponsors should consider whether remote assessments (e.g., phone or video) are appropriate for the type of clinical data that they plan to collect. For example, assessment of certain clinical items may require a greater degree of visual input than others and may be difficult to conduct remotely. In addition, sponsors considering use of remote ClinRO or PerfO assessments should determine whether it would be safe and feasible for the

[11] See 21 CFR 312.62(b) and 812.140(a)(3)
[12] See 21 CFR 50.27(a).
[13] See 21 CFR 50.20 and 50.27(a).
[14] See 21 CFR 50.27(a), 56.103(a), and 56.111(a).
[15] FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016, available at https://www.ncbi.nlm.nih.gov/books/NBK326791/. Co-published by National Institutes of Health (US), Bethesda (MD).

subject to participate in the assessment at their location (e.g., a 6-minute walk test might not be safe or the floor surface might not be consistent within the subject's home environment).

FDA recognizes that for a given trial, sponsors may be able to conduct assessments on some subjects on-site, whereas for other subjects, remote assessment may be necessary to adhere to public health measures implemented by Federal and State authorities to control the virus. In such cases, to minimize variability and ensure that remote assessments are comparable to on-site assessments, sponsors should perform the remote assessments in a manner as similar as possible to the assessments being conducted on-site, while protecting subject safety and privacy. For example, in a pediatric study, if a subject's assessment is done in the presence of the caregiver during the on-site assessment, it should also be done in the presence of a caregiver during the remote assessment to minimize unwanted variability. Increased variability in outcome measures could compromise data quality and limit FDA's ability to rely on the trial data for regulatory decisions.

When determining whether and how to conduct a remote assessment (e.g., by phone or video), sponsors should consider the rationale and information available to support the feasibility of the assessment. For example, sponsors should consider the feasibility of the assessment methods for use with subjects with disabilities (e.g., visual impairment). For PerfO assessments, sponsors should consider use of video to ensure that subjects are complying with the assessment instructions. To the extent feasible, sponsors should ensure that the methods and conduct of remote assessments are consistent across sites, subjects, and visits. For example, if a sponsor decides that video is their preferred method of remote assessment for use in a multi-site trial, using different modalities (e.g., both phone and video in the same trial) to conduct assessments may add unwanted variability.

Sponsors should also ensure that investigators are adequately prepared to perform remote assessments. For example, investigators could practice at least one (simulated) remote assessment before performing such assessments for a trial. The investigator should be prepared to assess and confirm with the subject that the setting in which the subject is participating is adequate to protect the subject's safety and privacy and to enable complete and accurate data collection.

To facilitate FDA's review of the data, for ClinRO and PerfO assessments, investigators should document, and sponsors should report in the clinical trial datasets, whether the assessment was conducted in-person or remotely (including type of technology used), as well as the date of the assessment and the person conducting the assessment.

Recognizing that components of the ClinRO or PerfO assessment for some trials may specify visualization or in-person interactions with subjects that may be difficult to replicate through remote interactions, sponsors should assess whether these components can be evaluated in an alternative way that still permits the assessment. When components of the assessment cannot be accomplished in a remote encounter, investigators should document and sponsors should report in the clinical trial datasets any aspects of the assessment they are unable to accomplish remotely. Sponsors should consider whether the information that can be collected remotely will be sufficient to accurately and reliably assess the clinical outcome to support robust conclusions for the study.

Sponsors planning to use remote assessments as part of a clinical investigation should develop procedures for provision of technical support to subjects and investigators to facilitate those assessments. For example, sponsors could develop a plan to accommodate subjects who are either already enrolled in a clinical trial or may be enrolled in a trial in the future, but who do not have

access to appropriate communication technology (e.g., cell phones or internet) by providing subjects with these services.

Sponsors should ensure that remote data acquisition, transmission, and storage are secure and protect subject privacy. When sponsors use electronic platforms designed to perform remote assessments, these platforms should include automated audit trails.

Q13. I am a study monitor and am unable to conduct on-site monitoring visits due to the COVID-19 public health emergency. May I remotely perform the site monitoring visit? What recommendations does FDA have for how I can remotely perform source document review?

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.[16] The regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches to monitoring that may vary depending on multiple factors. Therefore, certain aspects of site monitoring visits may be done remotely if technically feasible. FDA understands that there may be deviations from the timing of on-site monitoring visits set forth in the trial monitoring plan and procedures, and that sponsors may consider ways to replace on-site monitoring visits with remote monitoring visits during the COVID-19 public health emergency. Further, there may be components of an on-site monitoring visit, as outlined in the trial monitoring plan, that cannot be completed remotely.

During the COVID-19 public health emergency, traditional on-site monitoring might be difficult for reasons such as (1) sites may not be able to accommodate monitoring visits (e.g., due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. When planned on-site monitoring visits are not possible, the reason should be documented and available for review by the sponsor and during FDA inspections.

The sponsor should consider using a risk-based approach to prioritize sites for remote monitoring, including as many study sites as feasible (and with a frequency as close to that described in the site monitoring plan as feasible). The decision regarding which sites to prioritize for remote monitoring should be guided by centralized monitoring or other information available about site performance (e.g., frequency and severity of protocol deviations previously identified during monitoring visits or currently identified by centralized monitoring, number of randomized active trial participants, experience of site staff, known history of prior major audit or inspection findings).

Remote monitoring should be focused on review of critical study site documentation and source data. If the materials identified for review include participants' medical records that normally would be reviewed at the site (and such a review is consistent with the trial participants' informed consent documents) then, as discussed below, remote review of medical records may be explored with trial sites to complete source document review. When the study monitor cannot access the site to review critical source documents, requests for review of source documents that may include private health information should be consistent with requirements for source document validation and review as described in the current study monitoring plan or other appropriate study-specific document. When remote monitoring processes and procedures have not previously been described by the sponsor, these processes and procedures should be established (e.g., in a revised study monitoring plan or in

[16] See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

updates to existing sponsor policies and procedures).

During remote monitoring, the study monitor should focus on trial activities that are essential to the safety of trial participants and/or data reliability. Sponsors and monitors may wish to consider one or more of the following options to facilitate remote monitoring access to clinical site records:

- If the site can provide appropriate resources and technical capabilities, consider establishing a secure remote viewing portal that would permit site staff to provide access to the site's study documentation and/or trial participants' source documents for the study monitor's review. In addition, the potential for remote access to trial participants' electronic health records may be explored with trial sites.

- Sites could upload certified copies[17] of source records to a sponsor-controlled electronic system or other cloud-based repository that contains appropriate security controls. In the setting of a blinded or partially blinded study, if source documents contain potentially unblind information, controls to protect the study blind should be in place prior to transfer of source documents (e.g., use of an unblinded study monitor to review source documents, restricted access to folders containing copies of source documents). It is not necessary for the clinical site to have control of certified copies of source documents uploaded to such a repository; however, the clinical investigator should maintain control of the original source records.

Regarding retention of copies of source documents used for remote review, it would not be necessary to retain the certified copies of source documents used for remote review, provided the clinical investigator retains the original source documents according to FDA regulations for the retention of records.[18]

In addition, processes and procedures should be established for the handling of source document copies that were placed in temporary storage locations for remote review and that are no longer needed after the remote monitoring has concluded.

Remote monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities, and any resulting actions to address issues identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

[17] FDA guidance on Good Clinical Practice developed with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) describes a certified copy as "[a] copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original." See guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (February 2018) at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1.

[18] See 21 CFR 312.62, and 812.140(a)

Q14. I am a sponsor of commercial INDs and electronic common technical document (eCTD) requirements cannot be met due to the COVID-19 public health emergency. Who do I contact for assistance?

Commercial sponsors may qualify for a short-term waiver from the eCTD requirements under section 745A of the FD&C Act in unique and rare circumstances and for a limited duration. During the COVID-19 public health emergency, rare circumstances may arise in which a sponsor cannot meet eCTD requirements (e.g., if the current COVID-19 public health emergency has impacted computer operations). Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult the FDA electronic submission staff (contact information provided below) for technical assistance, rather than submitting a waiver request. As described in Section III.E of FDA's guidance *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*:

> FDA may grant temporary waivers of the requirement for eCTD submission if one or more of the following events or circumstances exist:
>
> - Extraordinary events or circumstances occur that are beyond the control of the submitter that justify a waiver, including but not limited to, natural disasters that impact computer operations.
> - An unplanned long-term internet disruption or other unplanned event occurs that would preclude the sponsor from submitting in eCTD format (e.g., malware attacks).
> - The sponsor intends to request a withdrawal of an application that has not yet converted to eCTD format.
> - The sponsor submitted a request for withdrawal and has not yet received FDA's acknowledgement of the withdrawal.[19]

The guidance also states:

> The sponsor or applicant's request to waive the eCTD electronic format requirement must include *all* of the following as supporting documentation to justify the waiver:
>
> (a) A description of the circumstances or event – including the anticipated duration of the circumstance or event – giving rise to the need for a waiver
> (b) The requested duration of the waiver
> (c) A description of the proposed alternative submission format the sponsor or applicant will be using for the duration of the waiver
>
> The request should reference all products that are to be covered by the waiver. The waiver request should be clearly titled "**WAIVER REQUEST – eCTD REQUIREMENTS**" in bold capital letters at the top of the first page of the submission.[20]

Waiver requests for new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), drug master files (DMFs), and commercial INDs may

[19] See guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications-0. To the extent that the guidance provides criteria for waivers and exemptions from the eCTD reporting requirements under section 745A(a) of the FD&C Act, it has binding effect pursuant to statute.

[20] Id.

be sent to FDA electronic submission staff via email to CDER (esub@fda.hhs.gov) or CBER (esubprep@cber.fda.gov). If a waiver is granted, FDA intends to provide information in the response letter on how to transmit the submission. FDA intends to encourage sponsors and applicants to send submissions electronically in an alternative electronic format (e.g., PDF files following the eCTD structure).

Q15. During the COVID-19 public health emergency, certain patients may no longer be able to travel to a central location for protocol-based treatment that is scheduled on a recurring basis. Can the investigational product intended for infusion be shipped to a local health care provider who is not a sub-investigator to administer the infusion to a patient while still maintaining integrity of the trial? If so, what else would be needed regarding trial monitoring and institutional review board (IRB) oversight?

Specific circumstances for a given clinical trial would affect the feasibility and appropriateness of shipping investigational products (IP) to locations other than clinical trial sites as specified under an IND, as well as administering the IP. If the IPs being evaluated in the trial are administered by infusion, then it would be important that any alternative infusion center have appropriately trained personnel and oversight by physicians with sufficient experience regarding the class of products involved to assure subject safety comparable to administration at a trial site.

For the purposes of this guidance, local health care providers (HCPs) who are administering drugs in a manner that does not differ from their normal clinical practices would not be considered sub-investigators and need not be listed on Form FDA 1572.[21] FDA recommends that these HCPs be listed in site records, such as a log of activities delegated by the investigator. Any changes to a trial protocol to permit an HCP to administer the investigational drug generally must be reviewed and approved by an IRB.[22]

The above paragraph described administration of the investigational product by local HCPs who are practicing medicine within their scope of practice. In contrast, if a sponsor will be asking local HCPs to perform study-specific research procedures or assessments that represent a direct and significant contribution to the clinical data for the study (e.g., assessing drug response for a patient or performing a procedure unique to the study and not part of routine medical care), these HCPs would be considered sub-investigators and should be listed on Form FDA 1572.

IP may be shipped from a central distribution site directly to an HCP, provided that such shipping is done under the supervision of the investigator using procedures that assure accountability and product quality (i.e., that storage conditions, as defined in the protocol, for the IP were maintained during shipping, and the drug packaging was intact upon receipt).

If the HCP administering the IP is not considered a sub-investigator, the investigator should ensure that they can obtain records regarding administration of the IP by requesting that the trial participants provide consent to allow access to medical records from their local HCPs involving trial-related data such as measuring vital signs, and results of evaluations of any symptoms or signs occurring with the

[21] For the definition of a sub-investigator, see 21 CFR 312.3(b); for the requirement to list sub-investigators on the FDA Form 1572, see 21 CFR 312.53(c)(1).

[22] As noted in the response to Q3 above, changes to a protocol necessary to eliminate an apparent immediate hazard to trial participants may be implemented before FDA and IRB review and approval. See 21 CFR 56.108(a)(4) and 21 CFR 312.30(b)(2)(ii).

infusion. Communicating the intent to request such records from the HCP in advance may facilitate this process.

Consulting the appropriate FDA review division(s) on plans for alternative administration is also recommended as per Q8 above.

Q16. If a subject is unable to receive the investigational drug from the trial site but the product is FDA-approved for other uses, can the patient or health care provider secure the product commercially or is this considered the sponsor charging for the investigational drug under 21 CFR 312.8? Can the sponsor reimburse trial subjects for their out of pocket expenses in getting the drug commercially?

If the product(s) under investigation in a clinical trial is FDA-approved, and the study does not require blinding, then local sourcing of the product(s) would be acceptable to FDA (e.g., by having the local physician write a prescription for the product instead of shipping the product directly to the patient). FDA does not consider a trial participant's commercial procurement of the study drug when unable to secure it from the trial site during the COVID-19 public health emergency to be a sponsor charging for an investigational drug under an IND per FDA regulations at 21 CFR 312.8. FDA also would not object if the sponsor reimburses the patient for any costs incurred by commercially purchasing the product or for charges related to an infusion.

Per FDA regulations at 21 CFR 312.6, the immediate package of an investigational new drug intended for human use must bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." FDA recognizes that a commercially obtained product will not have this statement on its container. In the setting of the COVID-19 public health emergency, where alternative arrangements are being made to provide an investigational agent to a participant who is unable to come to the trial site, FDA intends to exercise flexibility without sponsors needing to seek a waiver under 21 CFR 312.10 of the investigational labeling requirements under 21 CFR 312.6.

Q17. Throughout the guidance, FDA recommends that sponsors consult with the review division for certain changes to ongoing clinical trials. For drugs and biologics, is this a reference to scheduling a Type A meeting? How should sponsors contact FDA regarding device clinical trials?

As stated in our guidance *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*,[23] review division regulatory project managers (RPMs) are the primary point of contact for communications between a sponsor and FDA. Both FDA and sponsors use various communication methods to focus discussions to exchange information and resolve issues efficiently. For example, telephone communication between a sponsor and FDA RPM may be more effective for time-sensitive matters. FDA staff try to respond to sponsor questions promptly, while balancing FDA public health priorities and other work obligations. Note that to ensure participant safety, responses to safety-related inquiries will be prioritized over other inquiries. More generally, FDA understands that many questions that will arise regarding changes in trial conduct due to COVID-19 will need to be addressed expeditiously. RPMs will work with sponsors to determine the

[23] See guidance *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-communication-between-ind-sponsors-and-fda-during-drug-development.

best path forward to answer their questions for certain changes in an expedited manner.

To discuss urgent issues related to IDEs managed in CDRH, sponsors should contact the lead reviewer. For IDEs managed in CBER, sponsors should contact the RPM. For FDA feedback on a proposed future IDE study, or regarding modifications to ongoing studies that are not urgent (such as a statistical analysis plan to address missing data), a Pre-Submission is recommended. For additional information on Pre-Submissions, please refer to FDA's guidance *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program*.[24]

For general questions regarding FDA policy on clinical trial conduct during the COVID-19 public health emergency, sponsors should contact Clinicaltrialconduct-COVID19@fda.hhs.gov.

[24] See guidance *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (May 2019), *available* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.