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FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on April 2, 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 "Coronavirus Disease 2019 (COVID-19)," *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.

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FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic

Guidance for Industry, Investigators, and Institutional Review Boards

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

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 pandemic. The appendix to this guidance further explains those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 pandemic.

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 Services (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

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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, the Department of Health and Human Services (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 pandemic 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 product³, 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 control measures. Although the necessity for, and impact of, COVID-19 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 pandemic.

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. 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.

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- 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 IND or 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

⁴ 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).

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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).
- 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 are not already in place 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 pandemic:

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

⁵ See 21 CFR 312.30(b) and 21 CFR 812.35(a).

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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 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 pandemic, 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 pandemic?

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 pandemic 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

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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 pandemic?

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 pandemic 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 to 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 pandemic?

FDA recognizes that during the COVID-19 pandemic, sponsors of clinical trials may need to modify protocol-specified procedures. As in discussed in the main body of this guidance, for protocol deviations necessitated by the impact of the current COVID-19 pandemic, 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 (e.g., listing study reference number, patient ID, date of visit) that are deviations from the protocol due to the current COVID-19 situation generally would be acceptable.

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

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imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND or 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 the sponsor determines, based on credible information, 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 pandemic?

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), 21 CFR 312.30(b)(2)(ii), and 21 CFR 812.35(a)(2).

² See 21 CFR 312.30(b)(2).

³ See 21 CFR 312.62 and 21 CFR 812.140(a)(4).

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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, etc.), 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 pandemic, 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), 21 CFR 312.30(b)(2)(ii), and 21 CFR 812.35(a)(2).

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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 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 (21 CFR 312.60; 312.62, and 812.140). 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.⁵ 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.⁶

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 Investigational 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 treatment, 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 312.30(b) and 21 CFR 812.35(a).

⁶ See 21 CFR 312.30(b), 21 CFR 812.35(a), and 21 CFR 812.150(a)(4).

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Q9. Considering that there will be likely delays to on-site monitoring of clinical trials during the COVID-19 pandemic, 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 pandemic. 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 a signed informed consent from a patient who is in isolation and the COVID-19 infection control policy would prevent us from removing a document signed by the patient from their hospital room?

FDA regulations generally require that the informed consent of a participant be documented by the use of a written consent form 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.⁷

- If the technology is available, electronic methods of obtaining informed consent should be considered.⁸
- 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 health 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
 - 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

⁷ The procedures suggested do not apply to informed consent being obtained under 21 CFR 50.23 – (Exception from general requirements) or 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

⁸ 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>.

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- 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:

- Attestations 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. 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 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 consent from the participant's legally authorized representative in accordance with 21 CFR 50.27(a).