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# **Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency**

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## **Guidance for Industry, Investigators, and Institutional Review Boards**

**March 2020**

**Updated on December 4, 2020**

For questions on clinical trial conduct during the COVID-19 pandemic, please email [Clinicaltrialconduct-COVID19@fda.hhs.gov](mailto: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 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) (21 U.S.C. 371(h)(1)(C)) 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 web page 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 web page titled "Search for FDA Guidance Documents," available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an email request to [Clinicaltrialconduct-COVID19@fda.hhs.gov](mailto:Clinicaltrialconduct-COVID19@fda.hhs.gov) to receive an additional copy of the guidance. Please include the docket 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](mailto:Clinicaltrialconduct-COVID19@fda.hhs.gov).

*Contains Nonbinding Recommendations*

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION</b> .....	<b>1</b>
<b>II.</b>	<b>BACKGROUND</b> .....	<b>2</b>
<b>III.</b>	<b>DISCUSSION</b> .....	<b>3</b>
<b>IV.</b>	<b>ADDITIONAL RESOURCES</b> .....	<b>6</b>
	<b>APPENDIX: QUESTIONS AND ANSWERS</b> .....	<b>7</b>

# **Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency**

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## **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 office responsible for this guidance as listed on the title page.

### **I. Introduction**

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide general considerations to assist sponsors in assuring the safety of trial participants,<sup>1</sup> maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of 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.

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<sup>1</sup> In this document, the terms *trial participant* or *participant* are used and are interchangeable with the term *subject* as used in referenced FDA regulations.

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This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020 (85 FR 16949), 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.<sup>2</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.<sup>3</sup>

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,<sup>4</sup> or other considerations if site personnel or trial participants 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

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<sup>2</sup> Secretary of Health and Human Services Alex M. Azar II, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed ), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

<sup>3</sup> 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/>.

<sup>4</sup> For the purposes of this guidance, the term *investigational product* refers to human drugs and biological products, as well as medical devices.

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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.

### **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.

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- 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.<sup>5</sup> 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, 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.

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<sup>5</sup> See 21 CFR 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), and 812.35(a)(2).

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- 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).
- 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

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changes described above, a protocol amendment may be required under the applicable regulations.<sup>6</sup>

### **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 trial participant 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 public health emergency, please email [Clinicaltrialconduct-COVID19@fda.hhs.gov](mailto: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>.

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<sup>6</sup> See 21 CFR 312.30(b) and 812.35(a). Under applicable Federal regulations, investigators must engage with the Drug Enforcement Administration when amending protocols for research involving Schedule I substances under the Controlled Substances Act by requesting a modification to a site-specific investigator registration (see 21 CFR 1301.18).

*Contains Nonbinding Recommendations*

**Appendix: Questions and Answers**

Q1. Deciding whether to suspend, continue, or initiate trials .....	8
Q2. Deciding whether to continue administering product appearing to provide benefit .....	9
Q3. Managing protocol deviations and amendments .....	10
Q4. Submitting changes to IND and IDE protocol .....	11
Q5. Conducting remote (virtual) clinic visits.....	11
Q6. Capturing data on protocol and process deviations.....	12
Q7. Delivering low-risk investigational products to home .....	12
Q8. Disposal of unused investigational product.....	13
Q9. Changing site for delivering high-risk investigational product.....	14
Q10. Alternative monitoring approaches .....	14
Q11. Obtaining informed consent for patients in isolation .....	15
Q12. Obtaining informed consent from legally authorized representatives.....	17
Q13. Obtaining informed consent when electronic and paper forms cannot be provided .....	18
Q14. Remote clinical outcome assessments.....	20
Q15. Remote site monitoring visits.....	22
Q16. Challenges and temporary waivers for eCTDs.....	24
Q17. Shipping investigational product to local provider – Form 1572 and accountability .....	25
Q18. Use of commercial vs. investigational products.....	26
Q19. Scheduling of meetings with review divisions.....	27
Q20. Use of alternative laboratory or imaging centers .....	28
Q21. Use of video conferencing for trial visits .....	29
Q22. Postmarketing requirements for drugs, biologics, and devices .....	29
Q23. Reporting serious adverse events for approved drugs used to treat COVID-19 .....	31
Q24. Reporting serious adverse events associated with COVID-19 in a non-COVID trial .....	32
Q25. Reviewing IND safety reports .....	33
Q26. Collecting electronic signatures and Part 11 compliance.....	34

## *Contains Nonbinding Recommendations*

### **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

### *Contains Nonbinding Recommendations*

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.

## *Contains Nonbinding Recommendations*

### **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 (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. Protocol deviations should be included in final study reports and may also be included in annual reports.

For a study-wide change in protocol conduct, under the IND regulations 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 and notification to FDA through filing a protocol amendment to the IND.<sup>7</sup>

For studies under an IND, 21 CFR 312.30(b) specifies that sponsors must submit a protocol amendment to the IND describing any change in a phase 1 protocol that significantly affects the safety of trial participants or any change in a phase 2 and 3 protocol that significantly affects the safety of trial participants, 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 trial participant 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 after they are submitted to FDA and IRB approval has occurred.<sup>8</sup>

FDA recognizes that during the rapidly evolving circumstances of the current COVID-19 public health emergency, a sequence of changes may be needed to address those circumstances. Clinical investigators must document as protocol deviations any modifications to protocol-specified procedures that occur prior to IRB approval and submission of the protocol amendment implementing the modification.<sup>9</sup> Consolidating several protocol modifications in a single protocol amendment would be acceptable but should be submitted expeditiously.

For studies under an IDE, 21 CFR 812.35(a) generally requires prior FDA approval before implementing changes to the investigational plan. These requirements do not apply to changes made to protect the life or physical well-being of a trial participant in an emergency, including

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<sup>7</sup> See 21 CFR 56.108(a)(4) and 312.30(b)(2)(ii).

<sup>8</sup> See 21 CFR 312.30(b)(2).

<sup>9</sup> See 21 CFR 312.62.

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study-wide changes, but such deviations must be reported to FDA within 5 working days.<sup>10</sup> In addition, 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 trial participants 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 reports/notices within the required timeframe. Sponsors may consolidate implemented changes when submitting 5-day reports/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 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?**

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<sup>10</sup> See 21 CFR 812.35(a)(2).

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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 trial participants.<sup>11</sup> 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 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;

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<sup>11</sup> See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).

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these requirements must be addressed and documented.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup>

### **Q8. How can the sponsor ensure proper disposal of unused investigational drug product if the participant cannot return to the study site?**

FDA regulations outline sponsor and investigator responsibilities for storage conditions and accountability of investigational drug products, including disposition of unused investigational products (IPs).<sup>15</sup> Under 21 CFR 312.59, the sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator. The regulation further provides that the sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative does not expose humans to risks from the drug. The procedure for disposition is generally considered part of the investigational plan and is normally described in the study protocol as a study-specific plan for handling the IPs. In most protocols, such plans involve the participant bringing the unused IP to the clinical trial site and then the investigator returning the unused IP to the sponsor or its designee. During the COVID-19 public health emergency, if appropriate, a pre-paid shipping package can be used for the participant to return IP back to a central location where it can be accounted for and disposed of per the protocol, but this approach is not the only way to satisfy the regulatory requirements for disposition of unused IP. Regardless of the chosen disposition method, sponsors and investigators must maintain adequate records regarding the disposition of the IP.<sup>16</sup>

Sponsors may consider adopting alternative procedures for disposition of IP that permit sponsors and investigators to fulfill their requirements for maintaining adequate records of IP disposition (including documenting dates, quantity, and use by participants), provided such procedures do not expose humans to risks from the IP.<sup>17</sup> For example, it may be possible to provide the participants with a way to dispose of IP at their home (such as with a drug disposal pouch) and document such disposal through photo or video that can be transmitted to the investigator or sponsor. FDA does not endorse a particular approach, but the risks involved (e.g., environmental considerations) with specific IPs should be considered when selecting a method for disposal. FDA has provided a consumer update *Where and How to Dispose of Unused Medicines*<sup>18</sup> that provides recommendations to consumers about how to safely dispose of unused FDA-approved medication at home. Sponsors can consider whether any of those recommended methods of

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<sup>12</sup> See 21 CFR 312.60, 312.62, and 812.140.

<sup>13</sup> See 21 CFR 312.30(b) and 812.35(a).

<sup>14</sup> See 21 CFR 312.30(b), 812.35(a), and 812.150(a)(4).

<sup>15</sup> See 21 CFR 312.57, 312.59, 312.60, and 312.62.

<sup>16</sup> See 21 CFR 312.57 and 312.62.

<sup>17</sup> Sponsors should consider whether an information amendment should be submitted pursuant to 21 CFR 312.31.

<sup>18</sup> See <https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines>.

## *Contains Nonbinding Recommendations*

disposition are appropriate for approved drugs being studied for a new use in a clinical investigation. As noted in the consumer update, FDA only recommends flushing medications that are on the FDA flush list, which currently does not include unapproved IP.

Investigators proposing alternative disposition methods must obtain authorization of those methods from the sponsor of the trial.<sup>19</sup> Additional restrictions may apply to IPs subject to the Controlled Substances Act.<sup>20</sup>

### **Q9. 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. If a sponsor is considering providing alternative arrangements for administration of the investigational product (e.g., home nursing or alternative sites by trained but non-study personnel), the sponsor is expected to perform a risk assessment that considers the nature of the investigational product and the potential risks to both the trial participants and the health care providers responsible for administering the product at the alternative site. This risk assessment should include assessment of risk mitigation strategies. Based on this risk assessment, sponsors should consider whether consulting the appropriate FDA review divisions regarding plans for alternative arrangements for administration of investigational products that are usually administered in a health care setting is warranted.

Consulting FDA is 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.

### **Q10. 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

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<sup>19</sup> See 21 CFR 312.59 and 21 CFR 312.62.

<sup>20</sup> See 21 CFR 312.58(b) and 312.69

## *Contains Nonbinding Recommendations*

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.

### **Q11. How do I obtain signed informed consent from a hospitalized 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 (in this case, a hospitalized patient) be documented by the use of a written consent document that typically includes the elements of informed consent, as described in 21 CFR 50.25, and that has been approved by the IRB and signed and dated by the trial participant or their legally authorized representative at the time of consent (21 CFR 50.27(a)). When feasible, we recommend a traditional method of obtaining and documenting informed consent using a signed paper copy of the consent form, or use of electronic informed consent.<sup>21, 22, 23</sup> If neither of these approaches are possible, the following procedures would be considered to satisfy FDA's informed consent documentation requirement.<sup>24</sup>

#### **Method 1: A photograph of the signed informed consent document can be transmitted to the trial staff**

1. An unsigned consent form is provided to the patient by a person who has entered the room.
2. The investigator/designee arranges a telephone call or video conference call with the patient (and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin)).

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<sup>21</sup> See the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent in Clinical Investigations* (December 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fdaguidance-documents>.

<sup>22</sup> For example, for FDA-regulated trials conducted during the COVID-19 public health emergency, FDA has made the COVID MyStudies app available in the Apple App and Google Play stores as a platform enabling investigators to obtain informed consent securely from patients when face-to-face contact is not possible or practical due to COVID-19 public health measures to control the virus. To facilitate free use of the app during the public health emergency, FDA intends to fund the technical assistance required to operate the COVID MyStudies app, which will be provided by the Harvard Pilgrim Healthcare Institute, as resources permit. For more information, investigators interested in using the app should see <https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app>.

<sup>23</sup> See Q25.

<sup>24</sup> 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.

### *Contains Nonbinding Recommendations*

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 document with the patient by the investigator/designee and response to any questions the patient may have.
  - Verbal confirmation by the patient that their questions have been answered, 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.
4. The patient (or an individual in the room) takes a photograph of the signed informed consent document and sends it to the investigator/designee.
5. A trial team member enters the photograph into the trial records along with an attestation that states how that photograph was obtained and that it is a photograph of the informed consent document signed by the patient.

#### **Method 2: A witness can attest to the signature, but a photograph of the signed informed consent document cannot be transmitted**

1. An unsigned consent form is provided to the patient by a person who has entered the room.
2. The investigator/designee arranges a three-way telephone call or video conference call with the patient, a witness who is not otherwise connected with the clinical investigation, and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin). Alternatively, in lieu of using a witness, a recording of the conversation can be made.<sup>25</sup>
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 document with the patient by the investigator/designee and response to any questions the patient may have.
  - Verbal confirmation by the patient that their questions have been answered, 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.

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<sup>25</sup> If an investigator wants to record the telephone or video conference call, the investigator/designee should ensure that the recording is done in a manner consistent with applicable State and local laws and that all parties agree to being recorded.

## *Contains Nonbinding Recommendations*

4. When using a witness, documentation in the trial records includes: (1) a signed and dated attestation by the witness who participated on the call that the patient confirmed their agreement to participate in the trial and signed the informed consent document; and (2) a signed and dated attestation by the investigator/designee stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When using a recording in lieu of a witness, documentation in the trial records includes: (1) the recording of the conference call; and (2) a signed and dated attestation by the investigator/designee who participated on the call stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When either Method 1 or 2 is used to document informed consent, the resulting documentation should be: (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies),<sup>26</sup> and (2) retained according to applicable FDA record retention requirements as part of the trial record.<sup>27</sup>

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

### **Q12. 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,<sup>28</sup> 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 participant in the clinical investigation or is the legally authorized representative of the trial participant. For example, the consent form may be sent to the trial participant or their legally authorized representative by facsimile or email, and the consent interview may then be conducted by telephone when the trial participant or their legally authorized representative can read the consent form during the discussion. After the consent discussion, the trial participant or their legally authorized representative can sign and date the consent form.

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<sup>26</sup> FDA guidance on good clinical practice developed with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) defines 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 the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018), available on the FDA guidance web page.

<sup>27</sup> See 21 CFR 312.57, 312.62, and 812.140.

<sup>28</sup> See footnote 19.

## *Contains Nonbinding Recommendations*

Options for returning the document to the clinical investigator may include facsimile, a photographic image sent through electronic means, scanning the consent form and returning it through a secure email account, or posting it to a secure Internet address, especially if there are concerns about having the participant mail a potentially contaminated consent document. Alternatively, the trial participant 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 trial participant must document that informed consent was obtained prior to participation in the trial.<sup>29</sup> In addition, the person signing the consent form must receive a copy of the consent form.<sup>30</sup> Although FDA regulations do not require the trial participant's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.

The trial participant or their legally authorized representative must sign and date the informed consent form before the investigator may conduct any study-related procedures involving the participant.<sup>31</sup> Where it is not feasible for investigators to receive the signed consent form prior to beginning study-related procedures, the investigators should have the prospective trial participant or legally authorized representative confirm verbally during the consent interview that the participant or legally authorized representative has signed and dated the form. In addition, the overseeing IRB must review and approve the planned informed consent process.<sup>32</sup>

**Q13. How can informed consent be obtained and documented from a prospective trial participant (or legally authorized representative) when they cannot print and sign a paper copy of the consent form provided electronically by the investigator/designee, they cannot electronically sign the informed consent form, and providing a paper copy of the consent form via mail/courier is not feasible within the time frame for enrollment into the clinical trial?**

Where a prospective trial participant (or legally authorized representative) is unable to print the informed consent document provided electronically by the investigator/designee, an electronic signature process is not available, and the prospective trial participant must meet time-sensitive eligibility criteria, the investigator may consider using the following alternative process to satisfy FDA requirements for obtaining and documenting informed consent:

1. The investigator/designee provides the prospective participant (or legally authorized representative) with an electronic version of the informed consent document.
2. The investigator/designee arranges a telephone call or video conference call with the prospective participant (or legally authorized representative), the investigator/designee, a witness who is not otherwise connected with the clinical

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<sup>29</sup> See 21 CFR 312.62(b) and 812.140(a)(3)

<sup>30</sup> See 21 CFR 50.27(a).

<sup>31</sup> See 21 CFR 50.20 and 50.27(a).

<sup>32</sup> See 21 CFR 50.27(a), 56.103(a), and 56.111(a).

### *Contains Nonbinding Recommendations*

investigation and, if desired and feasible, additional participants requested by the prospective participant (e.g., next of kin). Alternatively, in lieu of using a witness, a recording of the conversation can be made.<sup>33</sup>

3. To ensure that the prospective participant (or legally authorized representative) is approached in a consistent fashion, a standard process should be used that will accomplish the following:
  - a. Identification of who is on the call.
  - b. Review of the informed consent document with the prospective participant (or legally authorized representative) by the investigator/designee and response to any questions the prospective participant (or legally authorized representative) may have.
  - c. Verbal confirmation by the prospective participant (or legally authorized representative) that their questions have been answered and that they would like to participate in the trial.
4. Verbal confirmation by the participant (or legally authorized representative) that they signed and dated a blank piece of paper with a written statement that they voluntarily agree to participate in the protocol, noting both the Protocol 'NUMBER' and brief protocol title.
5. After signing and dating the newly created document, the trial participant (or legally authorized representative) sends a photograph of the signed and dated statement by facsimile, text message, or email to the investigator/designee; OR returns the document to the investigator by mail at a later date, or at a future study visit that might occur in person.
6. When using a witness, documentation in the trial records includes a signed and dated attestation by the witness who participated on the call that the patient confirmed their agreement to participate in the trial and signed the document referenced above.
7. When using a recording in lieu of using a witness, documentation in the trial records includes the recording of the conference call.
8. After the signed and dated document is received by trial staff, it should be appended to a copy of the consent document that was reviewed with the trial participant (or their legally authorized representative) and retained in the trial records as would normally be done for a signed informed consent document.

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<sup>33</sup> If an investigator wants to record the telephone or video conference call, the investigator/designee should ensure that the recording is done in a manner consistent with applicable State and local laws and that all parties agree to being recorded.

## *Contains Nonbinding Recommendations*

Additionally, a note in the trial records should be made explaining the circumstances of why informed consent was obtained through an alternative method. The case history for each trial participant must document that informed consent was obtained prior to participation in the trial.<sup>34</sup>

This alternative approach must be reviewed and approved by the IRB overseeing the trial as required under FDA regulations.<sup>35</sup>

### **Q14. What factors should sponsors consider when deciding whether to change their clinical trial protocol during the COVID-19 public health emergency to include remote clinical outcome assessments?**

Some clinical outcome assessments (COAs)<sup>36</sup> can be conducted remotely in clinical trials during the COVID-19 public health emergency, including COAs for performance outcome (PerfO), interview-based clinician-reported outcome (ClinRO),<sup>37</sup> patient-reported outcome (PRO), and observer-reported outcome (ObsRO). During the COVID-19 public health emergency, sponsors may still be conducting in-person assessments on some trial participants, whereas remote assessments may be necessary for others to protect their safety or to respond to COVID-19-related public health measures implemented by government authorities to control the virus. When deciding whether to change their clinical trial protocols to include remote COAs, sponsors should evaluate the general and specific considerations outlined below.

General considerations regarding (1) prioritization of trial participant safety and privacy; (2) maintenance of data quality and integrity, including minimizing missing data; and (3) appropriate training for personnel and trial participants, which are discussed elsewhere in this guidance, are also common to all COAs. Other general considerations that are common to all COAs include attention to (1) the potential for increased variability in trial data; (2) the feasibility of conducting a specific type of COA remotely, depending on the context of use; (3) documentation and audit trails; and (4) availability of technology and technical support required for remote assessment. These considerations are explained in more detail below.

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<sup>34</sup> See 21 CFR 312.62(b) and 812.140(a)(3).

<sup>35</sup> See 21 CFR 50.27, 56.103, and 56.108(a).

<sup>36</sup> For purposes of this guidance, a *COA* is an assessment of a clinical outcome (i.e., an outcome that describes or reflects how a patient feels, functions or survives); a *ClinRO* is a measurement by a trained health care professional after observing a trial participant's health condition, a *PerfO* is a measurement based on a standardized task performed by a participant that is administered and evaluated by an appropriately trained individual or is individually completed, a *PRO* is a measurement based on a report that comes directly from the participant about the status of a patient's health condition without amendment or interpretation of the participant's response by a clinician or anyone else, and an *ObsRO* is a measurement based on a report of observable signs, events, or behaviors related to a participant's health condition by someone other than the participant or a health professional (e.g., a parent or caregiver). See 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).

<sup>37</sup> Non-interview-based ClinRO assessments, such as those reliant on diagnostic imaging or physical examination, present a distinct set of challenges and are not addressed in this guidance.

## *Contains Nonbinding Recommendations*

**Increased Variability in Data:** When switching from in-person to remote assessments, sponsors should perform remote assessments in a manner as similar as possible to those done in-person, while protecting trial participant safety and privacy. To the extent feasible, sponsors should ensure that the methods and conduct of remote assessments are consistent across sites, trial participants, and visits to minimize variability in the data. For example, if a sponsor decides that video is their preferred method of remote assessment in a clinical trial, then using different methods to conduct assessments (e.g., both telephone and video in the same trial) may increase variability. Maintaining consistency in assessment methods should be balanced, however, against the need to minimize missing data and the decision to use different methods should be justified in study documentation.

**Feasibility of the Assessment Method Within the Context of Use:** Investigators should assess the feasibility of conducting a specific type of COA remotely, which will depend on corresponding trial goals and needs (e.g., ability to conduct the assessment in a way that captures all the data needed to evaluate the endpoint in the trial), given that not all assessments can provide an accurate assessment when done remotely.

**Documentation and Audit Trails:** Investigators should document, and sponsors should include data on related variables in the clinical trial datasets, whether an assessment was conducted in-person or remotely (including type of technology used), as well as the date of the assessment and the person who conducted the assessment. Sponsors also should ensure that remote data acquisition, transmission, and storage are secure, and that the privacy of trial participants is protected. When sponsors use electronic platforms to perform remote assessments that transmit data directly into trial records, these platforms should include automated audit trails.

**Technology and Technological Support:** Sponsors planning to use remote electronic assessments as part of a clinical investigation should use appropriate technology and develop procedures for provision of technology and technical support to trial participants, investigators, and/or other trial personnel to facilitate those assessments. For example, sponsors could develop a plan to accommodate trial participants who are either already enrolled in a 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 trial participants with these services.

Specific considerations for certain COA types are explained below.

**PerfO- and Interview-Based ClinRO-Specific Considerations:** For these types of assessments, sponsors should consider: (1) appropriateness of remote assessment for the type of clinical data to be collected; (2) special investigator training to administer the PerfO or interview-based ClinRO assessments remotely; and (3) procedures for assessing and confirming the safety of trial participants, their privacy, and appropriate setting and resources to adequately complete the assessment.

Recognizing that components of the PerfO and interview-based ClinRO assessment for some trials may specify visualization or in-person interactions with trial participants 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 an accurate clinical

## *Contains Nonbinding Recommendations*

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 reliably assess the clinical outcome and support robust conclusions for the study.

**PRO- and ObsRO-Specific Considerations:** For these types of assessments, sponsors should consider: (1) potential for missing data when switching from in-person assessment to remote assessment; (2) whether switching from use of paper- or electronic-based PRO and ObsRO assessments completed independently to assessments administered verbally by another person may lead to bias of scores (e.g., if trial participants try to please the site staff by offering ratings that might not truly reflect their experience); and (3) that data collected with PROs and ObsROs through verbal administration should not be considered a substitute for required safety monitoring throughout the trial.<sup>38</sup>

To minimize potential bias resulting from verbal administration of PRO and ObsRO assessments, sponsors should ensure interviewer training and use of an interview script. Sponsors may also consider using automated virtual interviewers or a trained neutral third-party interviewer to administer the assessments remotely.

The potential for missing data is also a limitation when switching from in-person to remote assessment using paper-based PRO or ObsRO assessments, if the trial participant or observer fails to complete all or part of the questionnaire within a given timeframe. To mitigate potential for missing data, sponsors should consider remote electronic capture of these assessments through technologies that can remind trial participants to complete the questionnaires and/or verbal administration at the time instructed (assuming appropriate steps are taken to minimize bias from verbal administration).

**Q15. 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.<sup>39</sup> 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.

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<sup>38</sup> See 21 CFR 312.32(b), 312.56(c), and 812.46.

<sup>39</sup> See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

### *Contains Nonbinding Recommendations*

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 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<sup>40</sup> 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

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<sup>40</sup> See footnote 24.

### *Contains Nonbinding Recommendations*

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.<sup>41</sup>

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.

**Q16. 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 FDA's 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 for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Revision 7):

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).

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<sup>41</sup> See 21 CFR 312.62 and 812.140(a)

### *Contains Nonbinding Recommendations*

- 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.<sup>42</sup>

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.<sup>43</sup>

Waiver requests for new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), drug master files (DMFs), and commercial INDs may be sent to FDA electronic submission staff via email to CDER ([esub@fda.hhs.gov](mailto:esub@fda.hhs.gov)) or CBER ([esubprep@cber.fda.gov](mailto: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).

**Q17. 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

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<sup>42</sup> See the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Revision 7), available on the FDA guidance web page. 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.

<sup>43</sup> *Ibid.*

### *Contains Nonbinding Recommendations*

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 trial participant 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.<sup>44</sup> 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.<sup>45</sup>

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 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 Q9 above.

**Q18. If a trial participant 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 participants for their out of pocket expenses in getting the drug commercially?**

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<sup>44</sup> 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).

<sup>45</sup> 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)).

### *Contains Nonbinding Recommendations*

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.

**Q19. 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 for industry *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017),<sup>46</sup> 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 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 for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (May 2019).<sup>47</sup>

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<sup>46</sup> Available on the FDA guidance web page.

<sup>47</sup> Available on the FDA guidance web page.

## *Contains Nonbinding Recommendations*

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](mailto:Clinicaltrialconduct-COVID19@fda.hhs.gov).

**Q20. I am a sponsor and would like to use an alternate laboratory or imaging center<sup>48</sup> for protocol assessments. What should I consider regarding when this approach would be appropriate and the selection of alternate laboratories or imaging facilities?**

Given that trial participants may not be able to come to the investigational site for protocol-specified visits at which laboratory tests or imaging would be conducted, sponsors should evaluate whether it is feasible to use alternative laboratories or imaging centers. The suitability of such alternative arrangements may vary depending on whether the protocol-specified procedures are related to eligibility criteria, safety evaluations, or endpoint assessments.

In general, if trial participants cannot access a clinical trial site, alternative sites may be used for laboratory tests or imaging assessments that focus on the safety of trial participants when such tests and assessments are routinely performed in those settings (e.g., routine chemistries, blood counts, chest radiographs).<sup>49</sup>

However, if the results of laboratory tests or imaging assessments are the basis for formal hypothesis testing, including primary or secondary efficacy endpoints and some safety endpoints, sponsors should consult with the relevant FDA review division. For example, disparities in laboratory measurements or imaging protocols will introduce increased variability and thus can affect type I and type II error rates.

When baseline tests are necessary to characterize the eligible study population, potential variation in test performance or precision related to use of an alternative laboratory or imaging center may also warrant discussion with the FDA review division. For example, an inclusion criterion based on a commonly available, routine test performed as a safety screen (e.g., renal function on a metabolic panel) might be amenable to alternative laboratory collection with minimal impact on study results. Using an alternative laboratory for tests related to other eligibility factors could be more likely to affect study integrity (e.g., laboratory tests to identify a tumor biomarker required for inclusion, genetic test to identify a marker that is a critical inclusion criterion). It may be important for such assessments to be standardized at a single site or at most a few sites. Based on the nature of laboratory tests conducted for the purpose of protocol assessments, the alternative laboratory conducting such tests for investigational purposes will likely be subject to certification and other requirements under the Clinical Laboratory Improvement Amendments (CLIA).<sup>50</sup> Alternative laboratory and imaging centers may also be subject to additional laws governing their operations.

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<sup>48</sup> For IND studies, this would be laboratories and imaging centers not listed on the Form FDA 1572.

<sup>49</sup> If a local laboratory or imaging center will be used for certain patients and will not replace the laboratory and imaging center specified in the Form FDA 1572 for all patients, these alternative facilities do not need to be listed on the Form FDA 1572; it is sufficient to retain documentation of when such facilities were used for protocol specified tests. The sponsor can accumulate these changes and submit this information to the IND, in for example, an information amendment or a protocol amendment.

<sup>50</sup> For more information on CLIA, see <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf>.

## *Contains Nonbinding Recommendations*

### **Q21. We are instituting trial participant visits remotely through video conferencing. Are there recommendations regarding best practices?**

With the increasing use of telemedicine in clinical practice, a number of resources may be available to provide recommendations on best practices. FDA does not endorse any particular telemedicine best practices. However, from an FDA regulatory perspective, important considerations for trial visits through video conferencing include:

- The investigator or study personnel who will conduct remote visits should be trained on how to conduct real-time video conferencing visits (e.g., training on the use of telemedicine for remote clinical trial visits).
- Procedures should be put in place to maintain a trial participant's privacy, as would be done for a clinical visit.
- Both the investigator and the trial participant should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan developed by the sponsor.<sup>51</sup>

To provide the same information that would be documented during a face-to-face visit, the date of a real-time video conference visit should be documented in the trial records and, if specified in the protocol, the time of the visit. Investigators should consider asking for the trial participant's location during a video conference visit in case a medical emergency arises during the visit.

FDA considers real-time video interactions, including telemedicine, as a live exchange of information between the trial personnel and trial participants. These interactions are not considered electronic records and therefore are not subject to 21 CFR part 11.

### **Q22. How does the COVID-19 public health emergency affect drug and biological product clinical trials required as postmarketing requirements (PMRs)? What about for required postmarket device studies?**

The information in this guidance applies to all clinical trials, including those postmarketing clinical trials that FDA requires an applicant<sup>52</sup> to conduct<sup>53</sup> for drugs and biological products.

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<sup>51</sup> FDA does not endorse any specific identification method. Sponsors may consider the National Institute of Standards and Technology (NIST) Digital Identity Guidelines, Special Publication 800-63A—Enrollment and Identity Proofing Requirements When Developing an Identity Verification Plan, available at <https://pages.nist.gov/800-63-3/sp800-63a.html>.

<sup>52</sup> After a company submits a marketing application (e.g., new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), De Novo Classification Request, or premarket notification (510(k)) for review, the company is referred to as the *applicant*. The person who initiates a clinical investigation is referred to as the *sponsor* (see 21 CFR 312.3 and 812.3(n)).

<sup>53</sup> Specifically, this response is intended to apply to studies or clinical trials required under 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)), confirmatory trials for drugs approved under the accelerated approval pathway (21 U.S.C. 356(c)(2)(A)) and deferred pediatric studies (21 U.S.C. 355B).

## *Contains Nonbinding Recommendations*

Many of the considerations outlined in this guidance may also be relevant to postmarket device studies.<sup>54</sup>

Applicants who are required to complete postmarketing clinical trials for drugs or biological products follow a timetable that includes due dates for completing certain milestones in the trial. FDA encourages applicants to inform FDA as soon as possible if they experience COVID-19-related delays that may affect the applicant's ability to meet the applicable interim,<sup>55</sup> trial completion, and/or final report submission milestone(s). These applicants should propose feasible revised milestones for interim, trial completion, and/or final report submission milestone(s).<sup>56</sup>

For post-market device studies, the approved post-approval study protocol or post-market surveillance plan generally includes due dates for completing certain study milestones. Due dates for certain milestones may also be listed expressly in the order requiring the postmarket study. Applicants required to complete such studies should similarly inform FDA as soon as possible of COVID-19-related delays that may affect the applicant's ability to meet those milestones and propose feasible revised milestones.

Applicants with PMRs or required postmarket device studies should also provide an explanation to FDA of how COVID-19 impacts the ability to meet the original milestones. FDA will evaluate the facts and circumstances of the explanation provided, as well as the conduct of the applicant, in determining whether the applicant is in compliance with the applicable authority requiring the postmarketing trial or postmarket device study after the milestone has been missed.

Additional considerations for drug and biological product PMRs include:

- **PMRs Under Section 505(o)(3) of the FD&C Act.** FDA will continue to make “good cause” determinations on a case-by-case basis for all missed milestones, including those where the applicant asserts that its failure to meet a PMR interim, trial completion, and/or final report submission milestone(s) is related to the current public health emergency.
- **Deferred Pediatric Study PMRs Under the Pediatric Research Equity Act (PREA).**<sup>57</sup> If circumstances involving COVID-19 have affected an applicant's ability to complete a PREA PMR, applicants may request a deferral extension for

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<sup>54</sup> For devices subject to PMA, FDA may require post-approval studies as a condition of approval (21 CFR 814.82(a)(2)). FDA may also require manufacturers to conduct postmarket surveillance studies of certain class II and class III devices under section 522 of the FD&C Act (21 U.S.C. 360I).

<sup>55</sup> *Interim milestones* refer to those due dates scheduled to occur between the final protocol submission and trial completion milestones.

<sup>56</sup> Although a revised trial completion date may be acknowledged by FDA, for drugs and biological product PMRs, the original projected completion date will continue to be displayed on the FDA's Postmarket Requirements and Commitments web page.

<sup>57</sup> Section 505B(a)(3)(B) of the FD&C Act governs the process and timelines required for requests for a deferral extension for deferred pediatric studies required under section 505B of the FD&C Act (21 U.S.C. 355c) (often referred to as *PREA PMRs*).

## *Contains Nonbinding Recommendations*

the final report submission milestone. If an applicant has not obtained a deferral extension and fails to submit required PREA studies by the final report submission date listed in the PREA PMR, FDA is required to issue a non-compliance letter to the applicant.<sup>58</sup>

- **PMRs Under Accelerated Approval.** For confirmatory trials, if an applicant misses an interim, trial completion, and/or final report submission milestone, FDA will review the applicant's explanation for the delay, as well as assess the trial's progress prior to the current public health emergency, before determining whether or not the applicant has been compliant with its milestone obligations.
- **Annual Status Reports of PMRs.** Applicants must continue to follow the annual reporting requirements for PMRs<sup>59</sup> and should document in their annual status report the COVID-19-related reason(s) for missing interim, trial completion, and/or final report submission milestone(s), and any steps taken to address COVID-19-related factors.

**Q23. My company is the NDA holder of an FDA-approved drug for a non-COVID-19 indication and is also the sponsor of an IND for the same drug being investigated to treat COVID-19. If I receive a spontaneous report of a serious adverse event that occurred with the approved drug being used in clinical practice for treatment of COVID-19, do I report that event to the IND for the COVID-19 investigational use?**

Reports of serious adverse events (SAE) that occur *in clinical practice* with the use of an approved drug or biological product, whether or not the use is included in the labeling for that product, must be reported in accordance with the applicable post-marketing reporting requirements under FDA regulations at 21 CFR 314.80 and 600.80. Reports of SAEs for approved vaccines are submitted to the Vaccine Adverse Events Reporting System (VAERS), while reports of SAEs for other approved drugs and biological products are submitted to the FDA Adverse Event Reporting System (FAERS).<sup>60</sup>

Serious adverse events that occur *during a clinical trial* under an IND for an approved drug or biological product being investigated for a new use to treat COVID-19 must be reported as an IND safety report per FDA regulations at 21 CFR 312.32 if they are unexpected *and* the sponsor determines that there is a reasonable possibility that the drug caused the SAE.

Regardless of whether an SAE occurs in the course of clinical practice or during a clinical trial, and regardless of where it is first reported, an NDA or BLA holder who is also the sponsor of an IND investigating the same drug for COVID-19 is responsible for monitoring the safety of its

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<sup>58</sup> See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

<sup>59</sup> See section 506B of the FD&C Act (21 U.S.C. 356b), 21 CFR 314.81(b)(2)(vii), and 601.70(b).

<sup>60</sup> For more information, see the Vaccine Adverse Event Reporting System, available at <https://vaers.hhs.gov/reportevent.html>, and the FDA Adverse Event Reporting System (FAERS) Public Dashboard, available at <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>.

### *Contains Nonbinding Recommendations*

drug and evaluating all accumulating safety data.<sup>61</sup> If accumulating safety data, including use in clinical practice, indicates a new serious risk associated with the drug, an IND safety report will need to be filed to the IND, and updates will likely need to be made to the investigator brochure and/or the informed consent document.<sup>62</sup> For more information, see FDA's guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).<sup>63</sup>

**Q24. For a clinical trial that is *not* investigating treatments for COVID-19, if a trial participant diagnosed with COVID-19 experiences a serious adverse event associated with COVID-19 during the trial, should that be reported as an IND safety report? Should these events be reported to the IRB?**

Under FDA regulations at 21 CFR 312.32, a sponsor must report to FDA any serious adverse event (SAE) that is both unexpected and for which there is a reasonable possibility that the drug caused the serious adverse event, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event.

Given the community spread of infection during the COVID-19 public health emergency, trial participants in a clinical trial may be diagnosed with COVID-19 and experience SAEs associated with the disease that are not causally related to the investigational drug. However, it also is possible that an investigational drug might be causally related to a SAE associated with COVID-19 by making trial participants in the trial more susceptible to complications from COVID-19. Establishing this potential causal relationship likely requires more than a single or even a few cases. To determine whether a reasonably possible causal relationship exists between an investigational drug and an SAE in a randomized controlled trial, FDA recommends a comparison between the rate of observed SAEs among COVID-19 infected trial participants in the investigational drug arm to COVID-19 infected trial participants in the control arm. Given that such analyses entail examination of unblinded data, such assessments should be done only by a data monitoring committee that routinely reviews unblinded data or by a specially constituted safety committee that is appropriately “firewalled” and independent from those conducting the trial and performing other study analyses. If the latter, such a committee should review safety data only, not efficacy data. If the trial is not randomized, in some circumstances it may be warranted to determine whether there is an excess of SAEs in trial participants diagnosed with COVID-19 by comparing the rate of such events to an external similar population diagnosed with COVID-19, recognizing that the reported rates of SAEs and mortality in patients with COVID-19 have varied widely. In comparing the rate in the trial to the published literature, sponsors should consider reports in patients with similar comorbidities and levels of care. If the difference in SAEs across treatment arms or compared to an external population suggests a causal relationship between the investigational product and the SAEs in trial participants diagnosed with COVID-19, this finding must be submitted to FDA as an IND safety report in accordance with 21 CFR 312.32.

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<sup>61</sup> See 21 CFR 312.32(b).

<sup>62</sup> See 21 CFR 312.32(c).

<sup>63</sup> Available on the FDA guidance web page.

## *Contains Nonbinding Recommendations*

FDA had provided additional information about aggregate safety assessment and reporting for INDs in the guidance for industry and investigators, *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012),<sup>64</sup> and has proposed recommendations in the draft guidance for industry *Safety Assessment for IND Safety Reporting* (December 2015).<sup>65</sup>

Where an IND safety report is required to be submitted to FDA under 21 CFR 312.32, the investigator must also send that IND safety report to the IRB.<sup>66</sup> The IRB may have additional reporting requirements regarding COVID-19 during the clinical trial.

**Q25. Trial participants with COVID-19 may experience a number of serious and unexpected adverse clinical events, which may increase the volume of corresponding IND safety reports. If an investigator receives an IND safety report from a sponsor, is it acceptable to review only reports that the sponsor indicates will result in a change to the investigator brochure, informed consent, or protocol? Which IND safety reports must an investigator send to the IRB?**

No, it is not acceptable for an investigator to review only certain IND safety reports. Under 21 CFR 312.60, investigators are responsible for protecting the safety of trial participants in a clinical investigation. IND safety reports must be sent by the sponsor to FDA and all participating investigators<sup>67</sup> when the sponsor determines that a serious adverse event is unexpected and there is a reasonable possibility that the drug caused the serious adverse event, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event.<sup>68</sup> Reviewing IND safety reports is essential for protecting the safety of trial participants because a serious and unexpected adverse event represents a new potential risk associated with the investigational product. FDA considers the review of all IND safety reports critical to fulfilling investigators' responsibility to protect the safety of trial participants in a clinical investigation.<sup>69</sup>

In addition, investigators are required under 21 CFR 312.66 to report all "unanticipated problems involving risk to human subjects or others" to the IRB. FDA considers a serious and unexpected adverse event that meets the criteria for sponsor reporting to FDA and all investigators in an IND safety report under 21 CFR 312.32, and would generally consider a serious adverse event that meets the criteria for safety reporting for an IND-exempt bioavailability/bioequivalence study under 21 CFR 320.31(d)(3), to be an "unanticipated

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<sup>64</sup> Available on the FDA guidance web page.

<sup>65</sup> Available on the FDA guidance web page. When finalized, this guidance will represent FDA's current thinking on these issues.

<sup>66</sup> See 21 CFR 312.53(c)(1)(vii) and 312.66. See also the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009), available on the FDA guidance web page.

<sup>67</sup> See 21 CFR 312.32(c)(1).

<sup>68</sup> See 21 CFR 312.32. IND safety reports must be submitted as soon as possible, but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Unexpected fatal or life-threatening suspected adverse reactions must be submitted no later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)).

<sup>69</sup> See 21 CFR 312.60.

## *Contains Nonbinding Recommendations*

[problem] involving risk to human subjects or others” that therefore must be reported to the IRB by the investigator.<sup>70,71</sup>

For more information about safety reporting, see FDA’s guidances *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012)<sup>72</sup> and *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009).<sup>73</sup>

### **Q26. What considerations apply to the electronic systems used to generate electronic signatures on clinical trial records, including informed consent documents, during the COVID-19 public health emergency?**

Electronic systems<sup>74</sup> used to generate electronic signatures<sup>75</sup> on clinical trial records, including informed consent documents, during the COVID-19 public health emergency must comply with the requirements outlined in FDA regulations at 21 CFR part 11 (Part 11) when applicable.<sup>76, 77</sup>

FDA is aware that there are multiple commercial off-the-shelf (COTS) software systems providing electronic signature services for clinical trial records. FDA does not certify individual electronic systems or methods to obtain Part 11 compliant electronic signatures, but COTS vendors may be able to provide sponsors and other regulated entities with information regarding whether their systems are Part 11 compliant. When such information is unavailable from the vendor, and a Part 11 compliant electronic system is required, sponsors and other regulated entities must take other steps to ensure the electronic system or software in use is Part 11 compliant. For further information regarding Part 11 compliance, see FDA’s guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003)<sup>78</sup> and the additional recommendations proposed in the draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR Part 11—Questions and Answers* (June 2017).<sup>79</sup>

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<sup>70</sup> See 21 CFR 312.66.

<sup>71</sup> Many study protocols specify that the sponsor will submit IND safety reports to the IRB on the investigator’s behalf. In these situations, where the investigator receives confirmation that the report has been sent to the IRB (e.g., the investigator is copied on the report sent to the IRB by the sponsor), FDA does not intend to object to the sponsor submitting the report to the IRB on the investigator’s behalf and would not expect an investigator to provide the IRB with a duplicate copy of the report.

<sup>72</sup> Available on the FDA guidance web page.

<sup>73</sup> Available on the FDA guidance web page.

<sup>74</sup> For the purposes of this guidance, the term *electronic systems* means systems, including hardware and software, that produce electronic records.

<sup>75</sup> For the purposes of this guidance, the term *electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual’s handwritten signature (21 CFR 11.3(b)(7)).

<sup>76</sup> See 21 CFR 11.1(b). See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003), available on the FDA guidance web page.

<sup>77</sup> For records that are not subject to Part 11, sponsors and other regulated entities should rely on their internal business practices to determine acceptable electronic signature methods and controls.

<sup>78</sup> Available on the FDA guidance web page.

<sup>79</sup> Available on the FDA guidance web page. When final, this guidance will represent FDA’s current thinking on this topic.

### *Contains Nonbinding Recommendations*

When an electronic system that is Part 11 compliant is not available, regulated entities must have an alternate means of obtaining required signatures (e.g., handwritten<sup>80</sup> wet ink signatures executed on documents, handwritten stylus or finger-drawn signatures executed on electronic documents that are then printed or appropriately witnessed). Alternative methods for obtaining signatures on informed consent documents during the COVID-19 public health emergency are described in Q11 and Q12 of this guidance. When handwritten methods are used, the sponsor and other regulated entities should ensure that all records containing original handwritten signatures are (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies), and (2) retained according to applicable FDA record retention requirements.<sup>81</sup>

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<sup>80</sup> See 21 CFR 11.3(b)(8) for the definition of a *handwritten signature*.

<sup>81</sup> See 21 CFR 312.57, 312.62, and 812.140.