
Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

Guidance for Industry, Investigators,
and Institutional Review Boards

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. For questions regarding this document, contact (CDER) Office of Medical Policy, CDEROMP@fda.hhs.gov, 301-796-2500.

**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 Clinical Policy (OCLiP)**

**September 2023
Emergencies**

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

Guidance for Industry, Investigators, and Institutional Review Boards

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov

<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>
and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov

<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>
and/or

Office of Policy
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Room 5431
Silver Spring, MD 20993-0002
Email: CDRH-Guidance@fda.hhs.gov

<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products>

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 Clinical Policy (OCLiP)

September 2023
Emergencies

Contains Nonbinding Recommendations

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	DISCUSSION.....	2
	A. Considerations for Continuing Trials	2
	B. Policies and Procedures to Account for Potential Disruptions to Trials.....	4
	C. For All Trials That Are Impacted by a Disaster or PHE	4
	APPENDIX: Questions and Answers.....	6

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
Guidance for Industry, Investigators, and Institutional Review Boards¹

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

Disasters and public health emergencies (PHEs) have the potential to cause major disruptions in the conduct of clinical trials for medical products.² Such events can include (but are not limited to) hurricanes, earthquakes, military conflicts, infectious disease outbreaks, or bioterrorist attacks. FDA is issuing this guidance to provide general considerations to assist sponsors, institutional review boards (IRBs), and clinical investigators in assuring the safety of trial participants,³ maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during disasters and PHEs that may lead to major disruption of clinical trial conduct and operations. The appendix to this guidance further explains these general considerations in a question-and-answer format.

In general, FDA's guidance documents 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

¹ This guidance has been prepared by the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Oncology Center of Excellence, and the Office of Clinical Policy at the Food and Drug Administration.

² We note that *disasters* and *PHEs*, as those terms are used in this guidance, may include natural catastrophes (e.g., significant earthquakes) and other unanticipated, significant disruptions with the potential to substantially impact the conduct of clinical trials for medical products, including situations where the Secretary of the Department of Health and Human Services has declared a PHE under section 319 of the Public Health Service Act or has declared that circumstances exist justifying the authorization of medical products for emergency use under section 564(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

³ In this guidance, the terms *trial participant*, *participant*, and *subject* are interchangeable.

Contains Nonbinding Recommendations

the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA recognizes that disasters and PHEs can cause major disruptions to the conduct of clinical trials of medical products. For example, disasters or PHEs can lead to population quarantines, trial site closures, travel limitations, interruptions to the supply chain for the investigational product (IP),⁴ or other challenges related to the type of disaster or PHE (e.g., site personnel or trial participants infected during an outbreak). These challenges can create difficulties in complying with protocol-specified procedures, including administering or using the IP or adhering to protocol-specified visits and laboratory or diagnostic testing.

FDA is aware that not all trials can be initiated or continued during disasters and PHEs, and for some trials, there may be no alternative to stopping the trial earlier than planned in order to safeguard participants' and trial staff's safety. The determination of whether to continue a trial should be based first and foremost on ensuring that participants will continue to be able to participate safely. The determination should also consider whether the key objectives of the trial can still be met, with appropriate trial modifications implemented. FDA outlines the following general considerations to assist sponsors in ensuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity. The appendix further explains these general considerations by providing answers to questions that the Agency has received about conducting clinical trials during major disruptions.

III. DISCUSSION

A. Considerations for Continuing Trials

- Ensuring the safety of trial participants is paramount. Sponsors should consider above all whether participants can safely continue in the trial, including necessary modifications and risk mitigation steps to ensure safety. Sponsors should also consider whether the trial can continue to meet its key objectives with modifications that adequately address the disaster or PHE circumstances. Study⁵ decisions might include those regarding continuing trial recruitment, continuing use of the IP for participants already in the trial, and the need to change participant monitoring during the trial. In all cases, it is critical that trial participants, IRBs/independent ethics committees (IECs), and regulatory agencies are kept informed of changes to the design and conduct of the study as appropriate.

⁴ In this guidance, the term *investigational product* refers to investigational human drugs and biological products, as well as investigational medical devices.

⁵ In this guidance, the terms *trial* and *study* are interchangeable.

Contains Nonbinding Recommendations

- Sponsors should consider 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, discontinuing the administration or use of the IP, modifying the assessments or assessment schedule, or discontinuing participation in the trial. Such decisions will depend on specific circumstances, including the nature of the IP, the ability to conduct appropriate safety monitoring, the potential impact of the disaster or PHE on the IP supply chain, and the nature of the disease or condition under study in the trial. Sponsors should work with the investigators conducting the trial to assess the individual participant’s situation and risk profile when considering their status in the trial.
- Screening procedures (e.g., testing for an infectious disease) that may be mandated by the health care system in which a clinical trial is being conducted may not need to be included as an amendment to the protocol if the sponsor does not plan to incorporate the data collected as part of a new research objective.
- Changes to the protocol or investigational plan to eliminate apparent immediate hazards or to protect the life and well-being of research participants in an emergency may be implemented without IRB approval or before filing an amendment to the investigational new drug application (IND) or investigational device exemption (IDE) but are required to be reported afterwards.⁶ FDA encourages sponsors and investigators to work with their IRBs to prospectively define procedures as early as possible in response to major disruptions to ensure participant safety and to prioritize reporting of deviations necessitated by the impact of a disaster or PHE.
- The implementation of alternative processes for the conduct of the study 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 the disaster or PHE led to the changes in study conduct and the duration of those changes, indicate which trial participants were impacted, and document how those trial participants were impacted.
- There may be gaps in data capture, data loss, and difficulties in finalizing and locking datasets because of the disaster or PHE. If changes in the protocol will lead to amending data management, prespecified analyses, and/or statistical analysis plans, the sponsor should consider making such amendments in consultation with the applicable FDA review division. Before locking the database, sponsors should address how protocol deviations related to the disaster or PHE will be handled for the prespecified analyses in the statistical analysis plan.

⁶ See 21 CFR 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), and 812.35(a)(2).

Contains Nonbinding Recommendations

B. Policies and Procedures to Account for Potential Disruptions to Trials

- Sponsors, clinical investigators, and IRBs should consider establishing and implementing policies and procedures, or revising existing policies and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study. Changes to policies and procedures may address many issues, including the informed consent process; which participants can continue on the IP; study visits and procedures; data collection; study monitoring; adverse event reporting; study oversight; and changes in investigator(s), site staff, and/or monitor(s) due to travel restrictions, quarantine measures, or other safety measures. Policies and procedures should be compliant with applicable (regional or national) laws and regulations for the management and control of the disaster or PHE. Depending on the nature of the changes described above, a protocol amendment or IDE supplement may be required under the applicable regulations.⁷

C. For All Trials That Are Impacted by a Disaster or PHE

Sponsors should provide a description of the impacts on study conduct of the disaster or PHE in a study-specific document with references to appropriate sections of the clinical study report:

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of disaster- or PHE-related control measures
2. Specific challenges faced by the sponsor of the clinical trial as a result of the disaster or PHE
3. A listing of all participants affected by the disaster or PHE-related study disruption by unique trial participant number identifier and by investigational site and a description of how the individual's participation was altered, including missed visits and assessments related to the disaster or PHE
4. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from IP 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 or IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. FDA recognizes that protocol modifications might occur, including unavoidable protocol deviations

⁷ See 21 CFR 312.30(b) and 812.35(a). Under applicable Federal regulations, investigators who are conducting research with Schedule I controlled substances under the Controlled Substances Act must request prior approval from the Drug Enforcement Administration when seeking to conduct research beyond that which is described in the approved protocol (see 21 CFR 1301.18).

Contains Nonbinding Recommendations

due to the disaster or PHE, or control measures implemented in response to the disaster or PHE. Efforts to minimize impacts on trial integrity and to document the reasons for protocol deviations will be important.

Contains Nonbinding Recommendations

APPENDIX: Questions and Answers

Q1. Deciding whether to suspend, continue, or initiate trials	7
Q2. Managing protocol deviations and amendments	8
Q3. Submitting changes to IND and IDE protocol.....	9
Q4. Capturing data on protocol and process deviations	10
Q5. Conducting remote (virtual) clinic visits.....	10
Q6. Remote clinical outcome assessments.....	11
Q7. Use of alternative laboratory or imaging centers	14
Q8. Use of video conferencing for trial visits	15
Q9. Delivering low-risk IPs to home	16
Q10. Disposal of unused IP	16
Q11. Changing site for delivering high-risk IP	17
Q12. Alternative monitoring approaches	18
Q13. Remote site monitoring visits.....	20
Q14. Obtaining informed consent for patients who are physically isolated	21
Q15. Collecting electronic signatures and part 11 compliance.....	23
Q16. Challenges and temporary waivers for eCTDs.....	24
Q17. Shipping IP to local provider – Form FDA 1572 and accountability	25
Q18. Use of commercial versus IPs	26
Q19. Scheduling of meetings with review divisions.....	27
Q20. Postmarketing requirements for drugs, biologics, and devices	27
Q21. Reporting serious adverse events for approved drugs used to treat conditions related to a disaster or PHE.....	29
Q22. Reporting serious adverse events associated with conditions related to a disaster or PHE in a trial not related to the condition.....	30
Q23. Exclusion criteria for investigational medical products	31

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 a disaster or public health emergency (PHE)?

Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors 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 participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product (IP), the ability to conduct appropriate safety monitoring, the potential impact on the IP supply chain, each participant's underlying risk profile and situation during the disaster or PHE, and the nature of the disease or condition 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 disaster or PHE 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 availability of technology to communicate effectively and consistently with participants.
- 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 situation and its impact on staff availability. Important questions to be considered include: Are there appropriately trained staff that could be available to handle the expected tasks? Are 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 IP 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 administration 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.

Contains Nonbinding Recommendations

Important questions to be considered include: Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize disruptions to trial conduct?

- Assessing whether there will be continued operations of and adequate communications with institutional review board (IRB) or independent ethics committee (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 contingency and/or safety measures implemented by Federal, State, or local authorities.

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 ensuring the safety of trial participants, the DMC's assessment of the impact of modifications of trial conduct during a disaster or PHE is important to consider.

The risks and benefits of continuing a trial are likely different than a decision to initiate a trial. Given an 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 safety measures implemented by Federal, State, or local authorities.

Q2. How should sponsors manage protocol deviations and amendments to ongoing trials during a disaster or PHE?

FDA recognizes that during disasters or PHEs, 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 a disaster or PHE, 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 in disaster or PHE circumstances, use alternative documentation approaches. For example, if visits are to be conducted by telephone or 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 because of the disaster or PHE generally would be acceptable. Protocol deviations should be included in final study reports and may also be included in annual reports.

For changes in protocol conduct, under the investigational new drug application (IND) regulations, protocol amendments that are necessary to prevent apparent immediate hazards to trial participants can be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND.¹

¹ See 21 CFR 56.108(a)(4) and 312.30(b)(2)(ii).

Contains Nonbinding Recommendations

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 or 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 an emerging disease or condition related to the disaster or PHE 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.

Prior to IRB approval of an amendment and submission to the FDA, clinical investigators must document as protocol deviations any modifications to protocol-specified procedures.² Consolidating several protocol modifications in a single protocol amendment generally will be considered acceptable but should be submitted expeditiously.

For studies under an investigational device exemption (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 study-wide changes, but such deviations must be reported to FDA within 5 working days.³ 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 a disaster or PHE, we understand that it may be challenging to submit 5-day reports or notices within the required timeframe. Sponsors may consolidate implemented changes when submitting 5-day reports or notices and should update the IDE as soon as possible.

Q3. With the rapid changes in clinical trial conduct that may occur due to a disaster or PHE, including multiple deviations to address patient safety, what is the recommended way for sponsors and investigators to capture these data?

It is important to capture specific information for individual participants that explains the basis for missing protocol-specified information that includes the relationship to the disaster or PHE (e.g., from missed study visits or study discontinuations due to the event). This information, summarized in the clinical study report, will be helpful to FDA. If it is not possible to immediately 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.

² See 21 CFR 312.62.

³ See 21 CFR 812.35(a)(2).

Contains Nonbinding Recommendations

Q4. How should a sponsor submit a change in protocol that results from challenges related to a disaster or PHE?

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 – DISASTER OR PHE TYPE (e.g., HURRICANE, COVID-19)

TITLE OF PROTOCOL

Sponsors should summarize the major changes made to the protocol related to the disaster or PHE 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 disasters or PHEs upon submission to FDA if approved by the IRB.⁴ Sponsors seeking FDA input prior to implementation should indicate that in the cover letter.

For **IDE studies**, the sponsor should make a submission to its existing IDE, with the following information added to the cover letter in the subject line, as applicable:

CHANGE IN PROTOCOL SUPPLEMENT – DISASTER OR PHE TYPE (e.g., MILITARY CONFLICT or RADIATION EMERGENCY) or

NOTICE OF IDE CHANGE – DISASTER OR PHE TYPE (e.g., EARTHQUAKE or PANDEMIC), 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 participants without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of trial participants, and it will not impact data integrity?

FDA regulations allow for changes to be made to the 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 in an emergency.⁵ Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact

⁴ As noted in the response to Q2 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)).

⁵ See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).

Contains Nonbinding Recommendations

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 such 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, this could include documentation 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 will be 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), it is critical that the sponsor evaluate the potential impact of alternative approaches on participant safety and consider how to mitigate risks to participants, including whether to discontinue the IP.⁶

For IDE studies, sponsors are required to report deviations implemented to protect the life or physical well-being of a participant in an emergency to FDA within 5 working days after learning of the deviations.⁷ We recognize that challenges related to the disaster or PHE may make it difficult to meet this time frame. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. What factors should sponsors consider when deciding whether to change their clinical trial protocol to include remote clinical outcome assessments during a disaster or PHE?

Some clinical outcome assessments (COAs)⁸ can be conducted remotely in clinical trials, including COAs for performance outcome (PerfO), interview-based clinician-reported outcome (ClinRO),⁹ patient-reported outcome (PRO), and observer-reported outcome (ObsRO). During a disaster or PHE, investigators might still be conducting in-person assessments on some trial participants, whereas remote assessments may be recommended for others to protect their safety or to respond to measures implemented by Government authorities to protect the public. When

⁶ See 21 CFR 312.23(a)(6) and 812.25(c).

⁷ 21 CFR 812.35(a)(2).

⁸ In 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 *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 *ClinRO* is a measurement by a trained health care professional after observing a trial participant's health condition; 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, available at <https://www.ncbi.nlm.nih.gov/books/NBK326791>.

⁹ 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

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.

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 in the clinical trial datasets (1) data on variables related to the trial, (2) whether an assessment was conducted in-person or remotely (including type of technology used), and (3) the date of the assessment and the name of 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 use automated audit trails.¹⁰

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

¹⁰ See the guidance for industry *Computerized Systems Used in Clinical Investigations* (May 2007). 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-fda-guidance-documents>.

Contains Nonbinding Recommendations

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 technologies.

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 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.¹¹

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

¹¹ See 21 CFR 312.32(b), 312.56(c), and 812.46.

Contains Nonbinding Recommendations

bias from verbal administration). Investigators should record which assessments were conducted by alternative means on a participant level.

Q7. I am a sponsor and would like to use an alternate laboratory or imaging center¹² for protocol assessments. What should I consider regarding when this approach would be appropriate and how to select 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).¹³

However, if the results of laboratory tests or imaging assessments are the basis for evaluating important (e.g., primary or secondary) efficacy or safety endpoints, sponsors should consult with the relevant FDA review division before considering an alternative site. For example, differences in laboratory measurements or imaging protocols may introduce increased variability in analyses, which should be considered.

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 relevant 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 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

¹² For IND studies, this would be laboratories and imaging centers not listed on Form FDA 1572.

¹³ If a local laboratory or imaging center will be used for certain patients and will not replace the laboratory and imaging center specified in Form FDA 1572 for all patients, these alternative facilities do not need to be listed on 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.

Contains Nonbinding Recommendations

Improvement Amendments (CLIA).¹⁴ Alternative laboratory and imaging centers may also be subject to additional laws governing their operations. Investigators should record which assessments were conducted by alternative means on a participant level.

Q8. 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.¹⁵

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 11.¹⁶

¹⁴ For more information on the CLIA, see <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf>.

¹⁵ FDA does not endorse any specific identification method. Sponsors may consider the National Institute of Standards and Technology (NIST) Special Publication 800-63A, Digital Identity Guidelines: Enrollment and Identity Proofing Requirements, available at <https://doi.org/10.6028/NIST.SP.800-63a>.

¹⁶ See 21 CFR 11.1(b). See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003).

Contains Nonbinding Recommendations

Q9. If patients are currently dispensed IP 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?

Home delivery of IP that would not raise any new safety risks may be implemented to protect patients from risks associated with coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining IP storage conditions in accordance with the investigational plan and for IP accountability remain; these requirements must be addressed and documented.¹⁷ If the protocol indicates pharmacy dispensing for self-administration at home and this is changed to direct-to-patient shipments, then a protocol amendment¹⁸ or change to the investigational plan¹⁹ would be required to permit home delivery of the IP. 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 IP administration through protocol deviations may also be acceptable.²⁰ If the change in the mechanisms of IP distribution is then included in a submission to the existing IND or IDE, such a change may be part of a cumulative submission that includes a number of changes that accrue, rather than an urgent protocol change.²¹ Sponsors are also responsible for ensuring that home delivery does not compromise the quality of the product supplied.

Q10. 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 IPs.²² 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 a disaster or PHE, if appropriate, a prepaid shipping package can be used by the participant to return IP back to a central location where it

¹⁷ See 21 CFR 312.60, 312.62, 812.100 and 812.140.

¹⁸ See 21 CFR 312.30(b).

¹⁹ See 21 812.35(a).

²⁰ Investigators must not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects (21 CFR 56.108(a)(4), 312.66, and 812.35(a)). An amendment to the protocol should be considered if a protocol deviation is not isolated or transient. When impacting only a specific region or country, a country-specific amendment may be appropriate.

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

²² See 21 CFR 312.57, 312.59, 312.60, and 312.62.

Contains Nonbinding Recommendations

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.²³

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.²⁴ For example, it may be possible to provide the participants with a way to dispose of the 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 relevant considerations (e.g., environmental) associated 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*²⁵ 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 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.²⁶ Additional restrictions may apply to IPs subject to the Controlled Substances Act.²⁷

Q11. If participants are currently receiving an IP at the clinical trial site, can a sponsor switch to use at home?

Sponsors should consider the safety risk to trial participants who would miss receiving an IP because of the inability to come to the clinical trial site during a disaster or PHE. If a sponsor is considering providing alternative arrangements for administration of the IP (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 IP and the potential risks to both the trial participants and the health care providers (HCPs) responsible for administering the product at the alternative site. This risk assessment should include evaluation of risk mitigation steps. Based on this risk assessment, sponsors should consider consulting the appropriate FDA review divisions regarding alternative plans for the administration of IP that is usually administered in a health care setting.

²³ See 21 CFR 312.57 and 312.62.

²⁴ Sponsors should consider whether an information amendment should be submitted pursuant to 21 CFR 312.31.

²⁵ See <https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines>.

²⁶ See 21 CFR 312.59 and 21 CFR 312.62.

²⁷ See 21 CFR 312.58(b) and 312.69.

Contains Nonbinding Recommendations

Consulting FDA is strongly advised for complex IPs (e.g., cellular therapy and gene therapy products), where potentially altered storage and handling conditions could adversely affect product stability. However, in all cases, applicable requirements for maintaining IP storage conditions in accordance with the investigational plan (before and after reconstitution, if applicable), IP reconstitution specifications per the investigator's brochure, and IP accountability remain and must be addressed and documented.²⁸ Storage conditions and IP accountability should be considered if the protocol is amended to permit alternative site infusions. Defining circumstances when discontinuing IP administration, while continuing study participation, albeit with potentially delayed assessments, may be an appropriate option when suitable alternative arrangements for administration of the IP cannot be made.

Q12. Considering that there may be delays to on-site monitoring of clinical trials during a disaster or PHE, what are FDA's recommendations, including for remote monitoring, in such circumstances?

FDA recognizes that study monitors may not be able to access the trial sites for on-site visits in a timely manner during a disaster or PHE. 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, or remotely tracking trial participant status and study progress where appropriate and feasible.

Sponsors should carefully document situations where monitors were unable to access or had to delay monitoring of a clinical site. Sponsors or 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 may occur due to contingency and safety measures implemented and will consider these circumstances when evaluating inspectional observations.

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.²⁹ 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 can be done remotely if technically feasible. FDA understands that during a disaster or PHE, 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. Further, there may be components of an on-site monitoring visit, as outlined in the trial monitoring plan, that cannot be completed remotely.

During a disaster or PHE, 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

²⁸ See 21 CFR 312.60, 312.62, 812.100 and 812.140.

²⁹ See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

Contains Nonbinding Recommendations

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).^{30,31} The sponsors should also consider additional factors in any risk-based approach (e.g., underlying participant risk profile, type of medical product, ability to obtain the required data remotely). 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 are normally reviewed at the site (and such a review is consistent with the trial participants' informed consent documents), then, to complete source document review, remote review of medical records may be explored. 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 can be explored with trial sites.

³⁰ See the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

³¹ See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013).

Contains Nonbinding Recommendations

- Sites could upload certified copies³² 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 may contain unblinded information, controls to protect the study blind should be in place prior to transfer of source documents (e.g., use of an unmasked 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.³³

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.

Q13. During a disaster or PHE, some sponsors have used remote monitoring to oversee study conduct at clinical trial sites, including remote review of source data. Should data that have been remotely monitored be re-monitored during an on-site monitoring visit once the disaster- or PHE-related restrictions that prevented on-site monitoring visits have been lifted?

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.³⁴ These regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches that may vary depending on multiple factors. The guidances for industry *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013) and *A Risk-Based Approach to Monitoring of Clinical*

³² 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).

³³ See 21 CFR 312.62 and 812.140(a).

³⁴ See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

Contains Nonbinding Recommendations

Investigations: Questions and Answers (April 2023) clarify that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigations; these guidance documents also describe monitoring activities that reflect modern, risk-based approaches, including remote monitoring when appropriate.

The decision as to whether remote monitoring conducted for a given site or clinical investigation was adequate or should be followed up with additional on-site monitoring visits should be based on the sponsor's ongoing risk assessment. The sponsor may determine that on-site follow-up of remote monitoring activities is appropriate based on a risk assessment (e.g., sites with certain data anomalies or a higher frequency of errors, important protocol violations, or dropouts relative to other sites). As with on-site monitoring, remote monitoring should be focused on critical data and processes for human subject protection and trial integrity, such as the site's conduct of key study procedures and documentation related to important efficacy endpoints and safety assessments.

Q14. How do I obtain signed informed consent from a hospitalized patient who is in isolation during the disaster or PHE and is physically inaccessible because policies prevent trial staff from entering the patient's room due to a disaster or PHE?

FDA regulations generally require that the informed consent of a trial participant be documented by the use of a written consent document that typically includes the elements of informed consent, as described under 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.^{35,36} If neither of these approaches are possible, the following procedures would be considered to satisfy FDA's informed consent documentation requirement.³⁷

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 (e.g., by a health care worker who has entered the room).
2. The investigator or 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)).

³⁵ See the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016).

³⁶ See Q15.

³⁷ 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 prospective participants 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 or 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 or a recording can be obtained, but a photograph of the signed informed consent document cannot be transmitted

1. An unsigned consent form is provided to the patient (e.g., by a health care worker who has entered the room).
2. The investigator or 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.³⁸
3. To ensure that prospective participants 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 or 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.

³⁸ If an investigator wants to record the telephone or video conference call, the investigator or 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 or 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 or 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)³⁹ and (2) retained according to applicable FDA record retention requirements as part of the trial record.⁴⁰

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).

Q15. What considerations apply to the electronic systems used to generate electronic signatures on electronic clinical trial records, including informed consent documents, during a disaster or PHE?

Electronic systems⁴¹ used to generate electronic signatures⁴² on electronic clinical trial records, including informed consent documents, generally must comply with the requirements outlined in

³⁹ See footnote 32.

⁴⁰ See 21 CFR 312.57, 312.62, and 812.140.

⁴¹ For the purposes of this guidance, the term *electronic systems* means systems, including hardware and software, that create, modify, maintain, or transmit electronic records.

⁴² 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)).

Contains Nonbinding Recommendations

FDA regulations under 21 CFR part 11 (part 11).^{43,44}

FDA is aware that there are multiple commercial off-the-shelf (COTS) software systems providing electronic signature services for electronic clinical trial records. FDA does not certify individual electronic systems or methods to obtain part 11-compliant electronic signatures on electronic records, but COTS vendors may be able to provide sponsors and other regulated entities with information regarding whether their systems are part 11-compliant. Sponsors and other regulated entities should work with COTS vendors to ensure compliance with part 11. For further information regarding part 11 compliance, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003) and the additional recommendations proposed in the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers* (March 2023).⁴⁵

When a part 11-compliant electronic system used to create electronic signatures is not available, regulated entities must have an alternate means of obtaining required signatures⁴⁶ (e.g., handwritten⁴⁷ 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 are described in Q14 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.⁴⁸

Q16. I am a sponsor of commercial INDs, and electronic common technical document (eCTD) requirements cannot be met due to a disaster or PHE. Whom do I contact for assistance?

Commercial sponsors may qualify for a short-term waiver from the eCTD requirements under section 745A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in unique and rare circumstances and for a limited duration. During a disaster or PHE, rare circumstances may

⁴³ See 21 CFR 11.1(b), 11.10, and 11.30. See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003) and the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers* (March 2023). When final, this guidance will represent FDA's current thinking on this topic.

⁴⁴ For electronic 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.

⁴⁵ When final, this guidance will represent FDA's current thinking on this topic.

⁴⁶ See 21 CFR 50.27(a).

⁴⁷ See 21 CFR 11.3(b)(8) for the definition of a *handwritten signature*.

⁴⁸ See 21 CFR 312.57, 312.62, and 812.140.

Contains Nonbinding Recommendations

arise in which a sponsor cannot meet eCTD requirements (e.g., if computer operations are impacted). For information on requesting a short-term waiver from eCTD requirements, see section III.E of the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD guidance) (February 2020).

Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA's electronic submission staff for technical assistance, rather than submitting a waiver request, as described in section III.E of the eCTD guidance.

Q17. During a disaster or PHE, participants may no longer be able to travel to a central location for administration of an investigational drug that is scheduled on a recurring basis. Can the IP be shipped to a local HCP who is not a sub-investigator to administer the product to a participant while still maintaining integrity of the trial? If so, what else would be needed regarding trial monitoring and IRB oversight?

Specific circumstances for a given clinical trial would affect the feasibility and appropriateness of shipping IP to locations other than clinical trial sites as specified under an IND, as well as administering the IP. Depending on how the IP(s) being evaluated in the trial are administered, it would be important that any alternative location 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.

In this guidance, local 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 1572.⁴⁹ 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 HCPs to administer the investigational drug generally must be reviewed and approved by an IRB.⁵⁰

The above paragraph describes administration of the IP 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 that must be listed on Form FDA 1572.⁵¹

⁴⁹ 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)(viii).

⁵⁰ As noted in the response to Q2 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)).

⁵¹ 21 CFR 312.53(c)(1)(viii).

Contains Nonbinding Recommendations

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 ensure 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 receiving the product. Communicating to the HCP the intent to request such records in advance may facilitate this process.

Consulting the appropriate FDA review division on plans for alternative administration is also recommended as per Q11 above.

Q18. If a trial participant is unable to receive the IP from the trial site but the medical product is legally marketed in the United States for other uses, can the participant or HCP secure the product commercially? Can the sponsor reimburse trial participants for their out-of-pocket expenses in getting the product commercially?

If the product under investigation in a clinical trial is legally marketed and the study does not require blinding, then local sourcing of the product 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 participant). Depending on the circumstances for providing the commercially obtained drug to the participant, the sponsor may need to submit a request to charge for the investigational drug under 21 CFR 312.8(a)(3) and satisfy other applicable requirements under 21 CFR 312.8. FDA also would not object if the sponsor reimburses the participant for any costs incurred by commercially purchasing the product or for charges related to the use of the product (e.g., charges related to an infusion).

Per FDA regulations under 21 CFR 312.6, the immediate package of an investigational new drug intended for human use must include a label with the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” Per FDA regulations under 21 CFR 812.5, an investigational device or its immediate package for human use must include a label with the statement “CAUTION—Investigational device. 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 a disaster or PHE, where alternative arrangements are being made to provide a commercially obtained investigational drug to a participant who is unable to come to the trial site, FDA does not intend to object to the labeling of the investigational drug because it does not include the statement required under 21 CFR 312.6 and the sponsor has not obtained a waiver of that requirement under 21 CFR 312.10. In addition, FDA similarly does not intend to object to the labeling of a commercially obtained investigational device because it does not include the statement required under 21 CFR 812.5 and the sponsor has not obtained a waiver under 21 CFR 812.10.

Contains Nonbinding Recommendations

Q19. Throughout the guidance, FDA recommends that sponsors consult with the review division for certain changes to ongoing clinical trials. For drugs and biological products, is this a reference to scheduling a Type A or Type 1 meeting? How should sponsors contact FDA regarding device clinical trials?

As stated in our guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017), 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 arise regarding changes in trial conduct due to a disaster or PHE 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 the guidance for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).

For general questions regarding FDA policy on clinical trial conduct during a disaster or PHE, sponsors should contact CTconductquestions@fda.hhs.gov.

Q20. How are drug and biological product clinical trials required as postmarketing requirements (PMRs) affected during disasters or PHEs? What about required postmarket device studies?

The information in this guidance applies to all clinical trials, including those postmarketing clinical trials that FDA requires an applicant⁵² to conduct⁵³ for drugs and biological products.

⁵² 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)).

⁵³ 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)), deferred pediatric studies (21 U.S.C. 355B), and postmarketing studies required for drugs and biological products developed under the Animal Rule (see 21 CFR 314.610(b)(1) and 610.91(b)(1)); see also the FDA guidance for industry *Product Development Under the Animal Rule* (November 2015).

Contains Nonbinding Recommendations

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

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 delays due to a disaster or PHE that may affect the applicant's ability to meet the applicable interim,⁵⁵ trial completion, and/or final report submission milestones. These applicants should propose feasible revised milestones for interim, trial completion, and/or final report submission milestones.⁵⁶

For postmarket device studies, the approved postapproval study protocol or postmarket 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 delays due to a disaster or PHE that may affect the applicant's ability to meet those milestones and propose feasible revised milestones.⁵⁷

Applicants with PMRs or required postmarket device studies should also provide an explanation to FDA of how the disaster or PHE 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 an original 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,

⁵⁴ For devices subject to premarket approval, FDA may require postapproval 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).

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

⁵⁶ 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. In the case of Pediatric Research Equity Act postmarketing requirements, if a deferral extension is granted and the final report submission date has been deferred, the new final report submission date will replace the original or previously granted final report submission date.

⁵⁷ See the guidance for industry and FDA staff *Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act* (October 2022). See also the guidance for industry and FDA staff *Procedures for Handling Post-Approval Studies Imposed by PMA Order* (October 2022).

Contains Nonbinding Recommendations

trial completion, and/or final report submission milestone is related to the disaster or PHE.⁵⁸

- **Deferred Pediatric Study PMRs Under the Pediatric Research Equity Act (PREA):**⁵⁹ If circumstances involving a disaster or PHE have affected an applicant's ability to complete a PREA PMR, applicants may request a deferral extension of the timeline for a deferral granted by FDA. 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 noncompliance letter to the applicant.⁶⁰
- **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 before the disaster or PHE, 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 PMRs⁶¹ and should document in their annual status report the disaster or PHE-related reasons for missing interim, trial completion, and/or final report submission milestones, the reasons for the non-compliance with the milestones, and any steps taken to address factors specific to the disaster or PHE.

Q21. My company is the holder of an approved marketing application for an FDA-approved drug for a specific indication and is also the sponsor of an IND for the same drug being investigated for a new indication to prevent conditions related to a disaster or PHE. If I receive a spontaneous report of a serious adverse event (SAE) that occurred with the approved drug being used in clinical practice for the prevention of the disease or condition related to the disaster/PHE, do I report that event to the IND?

Reports of SAEs that occur in clinical practice with the use of an approved drug or biological product, whether or not the use is included in the approved labeling for that product, must be reported in accordance with the applicable postmarketing reporting requirements under 21 CFR 314.80 and 600.80. Reports of SAEs for approved vaccines are submitted to the Vaccine

⁵⁸ See the FDA guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

⁵⁹ Section 505B(a)(4)(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*).

⁶⁰ See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

⁶¹ See section 506B of the FD&C Act (21 U.S.C. 356b) and 21 CFR 314.81(b)(2)(vii) and 601.70(b).

Contains Nonbinding Recommendations

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).⁶²

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 or prevent a disaster- or PHE-related disease or condition must be reported as an IND safety report per FDA regulations under 21 CFR 312.32 if (1) they are unexpected and (2) 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 treatment or prevention of a disaster- or PHE-related disease or condition is responsible for monitoring the safety of its drug and evaluating all accumulating safety data.⁶³ If accumulating safety data, including use in clinical practice, indicates a new potential 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.⁶⁴ For more information, see the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

Q22. If a trial participant experiences an SAE that may be associated with a disease or condition related to the disaster or PHE, should that be reported as an IND safety report? Should these events be reported to the IRB?

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

Participants in a clinical trial may be diagnosed with a PHE- or disaster-related disease or condition and experience SAEs associated with the disease or condition that are not causally related to the investigational drug. However, it is possible that such SAEs could be causally related to the investigational drug. Establishing a potential causal relationship likely requires more than a single or even a few cases.

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) and has proposed recommendations in the draft guidance for

⁶² 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>.

⁶³ See 21 CFR 312.32(b).

⁶⁴ See 21 CFR 312.32(c).

Contains Nonbinding Recommendations

industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021).⁶⁵

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.⁶⁶ The IRB may have additional reporting requirements regarding the disaster or PHE that apply during the clinical trial.

Q23. Certain clinical trial protocols have an exclusion criterion for receipt of another investigational medical product. If a participant receives a vaccine or other medical product authorized under an emergency use authorization (EUA), would FDA consider this receipt of an investigational medical product?

When a medical product is being used under an EUA, it is an authorized (though not an approved or cleared)⁶⁷ medical product for use in clinical care that has met the statutory criteria under section 564 of the FD&C Act.⁶⁸ The product is not being studied under an IND or IDE when used pursuant to an EUA, and FDA therefore does not consider an individual's receipt of the product under an EUA as receipt of an IP. In contrast, when the same product is used in a clinical investigation under an IND or IDE, the product's safety and/or effectiveness is being studied for investigational uses, and FDA would consider receipt in this situation to be receipt of an IP.

In the design of a clinical investigation, there may be valid scientific reasons to have an exclusion (and even a discontinuation of study treatment) criterion for receipt of a medical product — a monoclonal antibody or vaccine, for example — whether that product was used under an EUA or not. These scientific reasons may include risks to an individual if they enroll or continue to receive study treatment in a clinical trial after receiving (or having received) the excluded product or the potential impact of the use of the excluded product on trial objectives, such as confounding the determination of effectiveness of the product under investigation.

⁶⁵ When final, this guidance will represent FDA's current thinking on this topic.

⁶⁶ 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).

⁶⁷ In this guidance, *approved or cleared*, with respect to devices, refers to FDA permitting the marketing of a device via the premarket approval, premarket notification (510(k)), De Novo classification, or Humanitarian Device Exemption (HDE) pathways.

⁶⁸ See section 564(k) of the FD&C Act (21 U.S.C. 360bbb-3(k)); see also guidance for industry *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).