Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

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Decentralized Clinical Trials for Drugs, Biological Products, and Devices
Guidance for Industry, Investigators, and Other Stakeholders[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This draft guidance provides recommendations for sponsors, investigators, and other stakeholders regarding the implementation of **decentralized clinical trials** (**DCTs**)[2] for drugs, biological products, and devices.[3,4,5] In this guidance, a DCT refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites.

In fully decentralized clinical trials, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes.

FDA's regulatory requirements for investigations of medical products are the same for DCTs and traditional site-based clinical trials.[6] Section 3606(a) of the Food and Drug Omnibus Reform

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Oncology Center of Excellence (OCE) at the Food and Drug Administration.

[2] Words and phrases in **bold** are defined in the Glossary.

[3] See section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(g)) for the definition of a *drug*. In this guidance, all references to *drugs* include both human drugs and biological products, unless otherwise specified.

[4] See section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)) for the definition of a *biological product*.

[5] See section 201(h) of the FD&C Act (21 U.S.C. 321(h)) for the definition of a *device*.

[6] See 21 CFR parts 312 and 812.

Act (FDORA) directs FDA to "issue or revise draft guidance that includes recommendations to clarify and advance the use of decentralized clinical studies to support the development of drugs and devices," not later than December 29, 2023. This guidance provides recommendations related to FDA's requirements for investigations of medical products when applied to DCTs and fulfills the requirement set forth in section 3606(a)(1) of FDORA. The content described in section 3606(b) of FDORA is further addressed through this guidance's reference to the draft guidance for industry, investigators, and other stakeholders entitled *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2021).[7]

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

II. BACKGROUND

Many clinical trials already include decentralized elements such that not all trial-related activities involving participants take place at traditional clinical trial sites. For example, laboratory tests are often conducted by **clinical laboratory facilities** at locations remote from traditional trial sites. DCTs have the potential to expand access to more diverse patient populations and improve trial efficiencies.[8] Advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (i.e., **telehealth**) allow for fewer in-person visits to clinical trial sites. **Digital health technologies** (**DHTs**), for example, have expanded the types of trial-related data that can be obtained remotely from trial participants. By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites. This may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.

Fully decentralized trials may be appropriate for **investigational products** (**IPs**) that are simple to administer or use, have well-characterized safety profiles (see section III.F), and do not require complex medical assessments. Alternatively, hybrid decentralized trials may be more appropriate in cases where the administration of an IP or a complex medical assessment needs to be performed at a clinical trial site and some follow-up assessments could be performed remotely through online patient-reported outcome measures, via telehealth or in-home visits, or by local health care providers (HCPs), as appropriate (see section III.B).

[7] When final, this guidance will represent FDA's current thinking on this topic. 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.

[8] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

Challenges related to DCTs may include coordination of trial activities with individuals and facilities in multiple locations that are not traditional clinical trial sites. DCTs generally include specific plans to facilitate the decentralization of the trial. These plans should include, as appropriate, the use of local health care facilities, local HCPs, and local clinical laboratory facilities; visits to trial participants' homes; and direct distribution of the IP to trial participants at their locations.[9] Specific issues related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with the relevant FDA review divisions.[10] Appropriate training, oversight, and up-front risk assessment and management will be key to implementing a DCT successfully.

III. RECOMMENDATIONS FOR IMPLEMENTING DCTS

The sections below provide guidance on specific topics for DCT implementation.

A. DCT Design

In a DCT, some or all trial-related activities will occur at locations other than traditional clinical trial sites (e.g., the participant's home or local health care facilities). DCTs may involve a network of locations where trial personnel and local HCPs work and where trial-related services (e.g., imaging and laboratory services) are provided, all under the oversight of the investigator.

For inspectional purposes, there should be a physical location where all clinical trial-related records for participants under the investigator's care are accessible and where trial personnel can be interviewed. This location should be listed on Form FDA 1572[11] or for investigational device exemption (IDE) applications must be included in the IDE application.[12]

The variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial. This would not affect the validity of a finding of superiority

[9] See 21 CFR 312.57(a), 312.62(a), 812.140(a)(2), and 812.140(b)(2) (describing requirements for disposition of the investigational product).

[10] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018). When final, these guidances will represent FDA's current thinking on these topics. See also the guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (January 2021). For applicants preparing abbreviated new drug applications (ANDAs), the Office of Generic Drugs in CDER encourages submission of controlled correspondence or a pre-ANDA meeting request to discuss the design, analysis, and implementation of a DCT before conducting the trial. See the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2022) (when final, this guidance will represent FDA's current thinking on this topic). For submitting a pre-ANDA meeting request, see the revised guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022).

[11] This information should be entered under Sections 1 and 3 on Form FDA 1572.

[12] See 21 CFR 812.20(b). The investigator's address is often the same as the location or institution where the trial is being conducted. However, if the addresses are different, both locations must be included in the IDE application.

in a trial using such data (although it could reduce the effect size), but it could affect the validity of a finding of non-inferiority.[13] Remote assessments may differ from on-site assessments, particularly when trial participants are responsible for performing their own physiological tests (e.g., home spirometry). Assessments performed by local HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel. In non-inferiority trials, when the effect size of an active control drug, for example, has only been determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT. This may present challenges in calculating a non-inferiority margin. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting.

B. Remote Clinical Trial Visits and Clinical Trial-Related Activities

Remote clinical trial visits and clinical trial-related activities are important strategies to make trials more convenient and more accessible to trial participants. The following should be considered when planning remote clinical trial visits or clinical trial-related activities:

- In general, investigators can consider telehealth visits instead of in-person visits with trial participants if no in-person interaction is needed.[14] The protocol should specify when a telehealth visit with a trial participant is appropriate and when a participant should be seen in person.

- In-person visits and trial-related activities can be conducted by trial personnel who are sent to participants' homes or preferred locations.

- Depending on the trial protocol, in-person visits and trial-related activities may also be conducted by HCPs who are located close to trial participants' homes but are not part of the trial personnel. These local HCPs (such as doctors or nurses) may be used by sponsors or investigators to perform certain trial-related activities; for example, on a fee-for-service basis. The trial-related services that they provide should not differ from those that they are qualified to perform in clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs). These services should not require a detailed knowledge of the protocol or the IP.

- Trial-related activities that are unique to research and/or require a detailed knowledge of the protocol or the IP should be performed by qualified trial personnel who have been appropriately trained. When applicable, both trial personnel and trial participants should be trained on how to conduct or participate in a telehealth visit.

[13] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[14] See 21 CFR parts 312 and 812.

- During each remote trial visit, investigators should confirm the trial participant's identity. FDA does not endorse any specific identification method. Sponsors and/or investigators can consider referring to existing digital identity guidelines.[15]

- Case report forms and other documentation should be completed for telehealth visits, including the date and time of the visit.

- The trial protocol should specify how adverse events identified remotely will be evaluated and managed. The protocol should describe how care will be provided for adverse events that require urgent or in-person attention. It is the sponsor and investigator's responsibility to ensure that remote clinical trial visits conducted via telehealth comply with laws governing telehealth in the relevant U.S. States or territories and other countries, as applicable.

C. Digital Health Technologies

DHTs may allow transmission of data remotely from trial participants wherever they are located. The sponsor should consider the following information regarding the use of DHTs in a DCT:

- The draft guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*[16] provides recommendations to sponsors, clinical investigators, and other parties for measuring clinical events and characteristics of interest using DHTs to acquire data remotely from participants in clinical trials for drugs, biological products, and devices. The guidance discusses selection of DHTs for clinical trials; verification, validation, and usability testing; use of DHTs to collect data for clinical trial endpoints; training on the use of DHTs; and management of risks related to the use of DHTs in clinical trials. Other issues regarding the use of DHTs in clinical investigations are discussed in other FDA guidances.[17]

- Sponsors should ensure that DHTs used in a DCT are available and suitable for use by all trial participants. When a trial permits participants to use their own DHTs, sponsor-provided DHTs should be available as an option to ensure that participants who do not

[15] See, for example, National Institute of Standards and Technology (NIST) Digital Identity Guidelines, NIST Special Publication 800-63A: Enrollment and Identity Proofing Requirements when developing an identity verification plan (https://pages.nist.gov/800-63-3/sp800-63a.html).

[16] When final, this guidance will represent FDA's current thinking on this topic.

[17] See the revised 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. For considerations on FDA's oversight of clinical decision support software, see the guidance for industry and FDA staff *Clinical Decision Support Software* (September 2022). For information on patient-reported outcomes and other clinical outcome assessments, see BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, 2016, available at https://www.ncbi.nlm.nih.gov/books/NBK326791.

have a protocol-specified DHT are not excluded from the DCT for that reason (e.g., lower socioeconomic groups who cannot afford the DHT).

D. Roles and Responsibilities

The roles and responsibilities of sponsors and investigators are described below.

1. The Sponsor

- Sponsor responsibilities are the same for DCTs and traditional site-based clinical trials.[18] Because DCTs may involve many contracted services, sponsors should ensure proper coordination of the decentralized activities (e.g., use of mobile nurses for at-home visits, use of local HCPs, direct shipping of IP to participants) (see sections III.B and III.G).

- Sponsors should strive for diversity and inclusiveness in trial populations.[19] Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of diverse participants in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes, including through the use of DHTs, may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may improve engagement, recruitment, and retention of diverse participants (e.g., race, ethnicity, age, sex, and geographic location). Further, the use of local HCPs may reduce cultural or linguistic barriers to participation in clinical trials.

- To account for multiple sources of data collection in a DCT, the sponsor should include at least the following in a **data management plan** (**DMP**):

  - Data origin and data flow from all sources to the sponsor (see section III.I) (e.g., a diagram that depicts the flow of data from creation to final storage)

  - Methods used for remote data acquisition from trial participants, trial personnel, and contracted service providers (e.g., local clinical laboratory facilities and local HCPs who perform trial-related activities)[20]

  - A list identifying vendors for data collection, handling, and management

[18] See 21 CFR parts 312 and 812.

[19] See the draft guidance for industry *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* (April 2022). When final, this guidance will represent FDA's current thinking on this topic.

[20] See the revised draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* and the draft guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* for recommendations related to storage and handling of data. When final, these guidances will represent FDA's current thinking on these topics.

- Sponsors should describe in the trial protocol how operational aspects of the DCT will be implemented. This description should cover, but may not be limited to, the following:
  - Scheduled and unscheduled clinical trial visits (remote and in-person, as applicable)
  - Transmission of reports on activities performed at different locations (e.g., medical imaging; clinical laboratory tests; and procedures performed at trial participants' home, work, or other local facility)
  - Delivery of IPs to trial participants, if applicable, and accountability for IPs
  - Safety monitoring and management of adverse events
- Case report forms should identify when and where data were collected and by whom.
- Sponsors must comply with relevant local laws, regulations, and licensing requirements governing medical practice and IP administration when conducting a DCT. This may involve addressing laws in multiple U.S. States, territories, and other countries.
- Sponsors must ensure proper monitoring of an investigation.[21] As with any trial, sponsors may use a variety of approaches to monitor DCTs, and the monitoring plan for a trial should be based on the sponsor's risk assessment.[22] A trial monitoring plan should (1) describe how monitoring will be implemented to assess protocol compliance and data quality and integrity, (2) specify the frequency with which trial records and source documents will be reviewed, and (3) note any unique aspects related to the DCT procedures. FDA encourages risk-based monitoring approaches and use of centralized monitoring to identify and proactively follow up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors.

2. The Investigator and Delegation of Trial-Related Activities

Investigators are responsible for the conduct of the DCT and the oversight of individuals delegated to perform trial-related activities, including ensuring that these delegated activities and/or tasks are conducted according to the investigational plan, applicable regulations, and

[21] See 21 CFR 312.50 and 812.40.

[22] For detailed information on risk-based approaches to monitor clinical trials, see the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

relevant laws.[23,24] A key difference between DCTs and traditional site-based clinical trials is the extent to which the investigator uses telehealth, trial personnel working remotely, local HCPs, and/or DHTs in the conduct of the trial. Whether the trial can be conducted entirely using remote visits or a hybrid trial design is appropriate depends on the types of assessments and procedures needed to collect endpoints and monitor safety. The decentralized features of the trial may necessitate additional training,[25] coordination, and standard operating procedures to ensure consistent implementation.

- When permitted by the trial protocol, investigators may delegate trial-related activities to local HCPs to perform trial-related procedures that require in-person interactions with trial participants (e.g., physical examinations and other medical procedures).[26] These procedures may take place at participants' locations or other local health care facilities as specified by the trial protocol.

- Videoconferencing and other technologies may be useful to allow investigators to oversee trial personnel performing activities described in the trial protocol (e.g., photographing lesions, fitting wearable sensors) at participants' locations.

- Investigators should enroll only as many trial participants as they can appropriately manage to ensure adequate supervision of DCT-related activities.

- As for any drug trial subject to 21 CFR 312.53, Form FDA 1572 must be completed by all investigators. The decision to include individuals as subinvestigators in a DCT should be based on their assigned responsibilities.

    - When trial personnel contribute directly and significantly to the trial data, they should be included on Form FDA 1572 as subinvestigators.[27]

    - Local HCPs contracted to provide trial-related services that are part of routine clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs) and where a detailed knowledge of the protocol, IP, and the investigator's brochure is not necessary should not be listed on Form FDA 1572

[23] See 21 CFR 312.60, 312.61, and 812.100.

[24] See the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects* (October 2009).

[25] See 21 CFR 11.10(i).

[26] See 21 CFR 312.3 and 812.3.

[27] See 21 CFR 312.3 and 312.53. For more information on subinvestigators, see questions 31 and 32 in the information sheet guidance for sponsors, clinical investigators, and IRBs *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* (May 2010) and the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Trial Subjects*.

as subinvestigators. However, local HCPs should be included in a task log (as described below in this section).

- For device investigations, investigator responsibilities under 21 CFR part 812 include the requirement that there be a signed agreement between the investigator and sponsor (see 21 CFR 812.43(c)(4) and 812.100). A list of all investigators in the study is also required as part of an IDE application (see 21 CFR 812.20 and 812.150(b)(4)). Local HCPs contracted to provide trial-related services that are part of routine clinical practice and where a detailed knowledge of the protocol or the IP is not required are generally not considered investigators and should not be included in the IDE list of investigators. However, these local HCPs should be included in a task log (as described below in this section).

- A critical consideration in a DCT when delegating trial-related activities to local HCPs is the potential for variability in the approach across different practices (e.g., documenting vital signs, physical examinations, and evaluation of adverse events). Quality control measures should be in place to help reduce variability, including regular review by investigators of participant data entered by local HCPs, to assess consistency and completeness of the required procedures. The type and scope of quality control measures should be tailored to the criticality of the data and the complexity of procedures done by the local HCPs.

- As part of preparing and maintaining adequate case histories,[28] investigators must maintain a task log of local HCPs who perform trial-related activities.

  - The task log should include (1) the names and affiliations of the local HCPs, (2) a description of their roles and assigned tasks, (3) the dates these local HCPs are added to the log, and (4) the locations where these activities are conducted.

  - The task log should be dated and signed by the investigator when initially created and updated when new local HCPs are added. The task log should be available to FDA during inspections.

  - Other health care professionals not involved in the clinical trial who deliver care to trial participants but not as part of the trial should not be listed on Form FDA 1572, the task log, or a medical device sponsor's current list of investigators. These professionals may include emergency room personnel, hospital personnel, family physicians, and nurses providing routine care for trial participants with emergent or existing conditions.

- Some trial protocols will include designated clinical laboratory facilities[29] to perform activities required by the protocol (e.g., phlebotomy, x-rays). Other trial protocols may

[28] See 21 CFR 312.62 and 812.140.

[29] See the information sheet guidance for sponsors, clinical investigators, and IRBs *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)*.

permit the use of a variety of clinical laboratory facilities close to the trial participant to perform these activities. Generally, designated clinical laboratory facilities are preferable to minimize variability, particularly for critical data such as those used to evaluate outcomes, and to perform investigations and tests that are specialized. If appropriate, specimens from trial participants (e.g., blood, sputum) may be collected by remote trial personnel, local HCPs, or clinical laboratory facilities and sent to designated facilities for processing. Local clinical laboratory facilities may be adequate for routine clinical tests that are well-standardized.

- All clinical laboratory facilities should be listed on Form FDA 1572 or in the investigational plan for device studies under an IDE.

- Technicians and other personnel working for clinical laboratory facilities should not be recorded on the task log or Form FDA 1572. However, for certain device studies (e.g., in vitro diagnostic devices), it may be necessary to identify the responsible individual at the laboratory facility where device testing is done in the task log or IDE application.[30]

- As in any trial, trial participants experiencing any health emergency (e.g., hypoglycemia or abnormal cardiac rhythm) should seek medical attention at local health care facilities (such as an emergency room), as appropriate. With the permission of trial participants, investigators should attempt to obtain reports from these local health care facilities, and investigators should also attempt to obtain reports from primary providers of routine health care when activities take place that are relevant to the trial (e.g., change in concomitant medications).

E. Informed Consent and Institutional Review Board Oversight

Obtaining informed consent remotely may be considered as part of a DCT. Institutional review board (IRB) oversight is required to ensure the process is adequate and appropriate.[31]

- Investigators may obtain electronic informed consent from trial participants at their remote locations provided that all applicable regulatory requirements regarding informed consent are met.[32] The process of obtaining electronic informed consent remotely may include a remote visit if needed.

[30] For certain device studies, the laboratory facility is a clinical trial site under 21 CFR part 812, and complete information on the site, including the investigator (i.e., responsible individual), is required in the IDE application and study records.

[31] 21 CFR 56.103, 56.104, and 56.105.

[32] For FDA regulations about informed consent, see 21 CFR part 50 (including the elements of informed consent under 21 CFR 50.25 and the documentation of informed consent under 21 CFR 50.27). For additional information, see the guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016).

- With a DCT, the informed consent process must include notifying participants of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject.[33]

- The informed consent should describe who will have access to the trial participant's personal health information obtained during the DCT.

- FDA recommends the use of a central IRB in DCTs to facilitate efficient review of the protocol, the informed consent documents, and other relevant trial-related information.[34]

F. Investigational Products in a DCT

1. Drugs and Biological Products

An investigator must administer an IP only to participants under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator.[35] The nature of the IP should be considered when determining whether administration outside of a clinical trial site in a DCT is appropriate. IPs that involve complex administration procedures; have a high-risk safety profile, especially in the immediate post-administration period; or are in early stages of development such that the safety profile is not well defined may need in-person supervision by the investigator at a trial site.

For IPs for which the safety profile is well-characterized and that do not involve specialized monitoring during the immediate period following administration, it may be appropriate for local HCPs or trial personnel working remotely to administer the IP at local health care facilities or participants' homes. Hybrid DCTs may be designed for drugs that require supervised but infrequent (e.g., monthly) administration when administration can be done at trial sites with follow-up done remotely.

Depending on the safety profile of the IP (e.g., a class of drug with a risk of hypersensitivity, abuse potential) and the type of trial (e.g., dose escalation trial), sponsors should estimate the urgency and complexity of care that may be needed based upon risks related to the IP and the participant's underlying condition. Investigators should take steps to help ensure that participants have access to an appropriate level of local care.

Drugs best suited for direct shipment to the participant's home include those with long shelf lives and those with good stability profiles. Drugs that involve specialized handling, shipping, and storage conditions may not be suited for direct shipment to locations outside the trial site.

[33] See 21 CFR 50.25(a)(7).

[34] See 21 CFR 56.114 (for a description of arrangements related to use of a central IRB). For additional information, see the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 2006).

[35] 21 CFR 312.61.

2. Medical Devices

When determining the appropriate use or administration of an investigational device in a DCT, sponsors should consider the type of medical device, its intended use, its instructions for use, and whether it is a significant risk or nonsignificant risk device.[36]

Medical devices suitable for home use (i.e., over-the-counter devices) that do not pose significant risks to trial participants may be appropriate for use by trial participants without the investigator's direct oversight. The use of medical devices that are not intended for self-use (i.e., devices used in hospital or ambulatory care settings) or that pose significant risks to trial participants should be used or administered by qualified trial personnel with investigator oversight. An investigator shall not supply an investigational device to any person not authorized under 21 CFR part 812 to receive it.[37] Certain follow-up procedures needed after using the medical device or after surgical implantation of the device in trial participants may be performed by appropriately qualified and trained local HCPs or trial personnel via telehealth visits, at the homes of trial participants, or in local health care facilities. A telehealth visit may be appropriate if an assessment in that setting does not pose significant risk to trial participants and, in such settings, adverse events can be (and are) properly assessed and documented.

G. Packaging and Shipping of Investigational Products

Generally, DCTs may allow for the direct distribution of investigational products to trial participants at their locations.[38] The sponsor should consider the following recommendations regarding packaging, shipping, and storage of IPs in a DCT:

- The protocol should describe how the physical integrity and stability of the IP will be maintained during shipment to trial participants, including appropriate packaging materials and methods (e.g., temperature control). Shipping containers should include clear instructions for handling and storing the IPs and instructions for returning unused IPs.[39, 40]

- When relevant, DCT personnel should be trained on procedures and appropriate documentation for handling, packaging, shipping, and tracking IPs.

[36] See the information sheet guidance for IRBs, clinical investigators, and sponsors *Significant Risk and Nonsignificant Risk Medical Device Studies* (January 2006).

[37] See 21 CFR 812.110.

[38] See 21 CFR 312.61.

[39] For information about packaging, labeling, and distribution of phase 1 investigational drugs and biological products, see section V.G in the guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008).

[40] For information about packaging and labeling operations of phases 2 and 3 investigational drug and biological products, see section VII in the guidance for industry *Preparation of Investigational New Drug Products (Human and Animal)* (reprinted November 1992).

- A central distribution service could be used to ship the IP directly to trial participants. The investigator or delegated trial personnel must control the release of the IP by the distributor; monitor receipt and use by trial participants (or participants' legally authorized representatives), according to procedures described in the protocol; and monitor the return or disposal of any unused product as directed by the sponsor.[41]

- The protocol should describe how investigators will track and document that trial participants (or participants' legally authorized representatives) receive IPs.

- The protocol should describe procedures that investigators or participants (or participants' legally authorized representatives) should use to return or dispose of unused IPs and how this will be documented.[42]

- Sponsors and investigators must comply with applicable Federal, State, and international laws and regulations that address shipping IPs in their respective jurisdictions.

H. Safety Monitoring Plan

The sponsor is required to ensure proper monitoring of the investigations and to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND or IDE applications.[43] Sponsors should implement a safety monitoring plan to ensure the safety and welfare of trial participants in a DCT.

- The safety monitoring plan should take the decentralized nature of the clinical trial into account and ensure that adverse events are appropriately captured and adequately addressed.[44] The monitoring plan should prespecify if and when telehealth visits or in-person visits (e.g., physical examinations) will be scheduled with trial personnel or local HCPs to collect safety data by (see section III.B).

- As in any site-based clinical trial, the safety monitoring plan should describe how participants are expected to respond to and report adverse events, including where to seek medical assistance locally when necessary and where to receive follow-up care.[45]

[41] See 21 CFR 312.61, 312.62(a), and 812.110.

[42] See 21 CFR 312.62(a) and 812.110(e) (for requirements related to disposition of the IP).

[43] 21 CFR 312.50 and 812.40. See also the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013).

[44] Certain late-stage pre-approval or post-approval clinical trials could be able to use selective safety data collection. See the ICH guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022).

[45] For information about the medical care of trial subjects, see section 4.3 in the guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

- Trial participants must be able to contact trial personnel to report adverse events and to have pertinent questions answered.[46]

- Trial participants should be able to arrange for an unscheduled visit using telehealth or an in-person visit, as appropriate (see section III.B).

- The safety monitoring plan should describe the type of information that will be collected by a DHT (when used to collect data in a DCT), how that information will be used and monitored, and what action trial participants or personnel should take in response to abnormal findings or electronic alerts.

- If significant safety risks emerge because of the remote administration or use of an IP, sponsors must discontinue remote administration or use; notify FDA, the IRB, and all investigators who have participated in the trial; and determine if the trial should continue.[47]

- If authorized in the protocol, routine safety monitoring involving laboratory testing and imaging may be performed using local clinical laboratory facilities close to trial participants (see section III.D.2). Investigators should ensure they promptly receive reports of these services and review them in a timely manner.

I. Software Used in Conducting DCTs

Sponsors should consider the following regarding software used in a DCT:

- Software to support the conduct of DCTs can be run through a variety of platforms (e.g., tablets, cell phones, personal computers). Software can be used to perform multiple functions to manage DCT operations, including:

  - Managing electronic informed consent (e.g., maintaining approved versions of informed consent, documenting IRB approval, archiving signed forms)

  - Capturing and storing reports from remote trial personnel, local HCPs, and local clinical laboratory facilities

  - Managing electronic case report forms (eCRFs)

  - Scheduling trial visits and other DCT-related activities

  - Tracking IPs that are shipped directly to trial participants

[46] See 21 CFR 50.25(a)(7).

[47] See 21 CFR 312.56(d) and 812.46.

  - Syncing information recorded by DHTs

  - Serving as communication tools between DCT personnel and trial participants

- Training should be provided to all parties (e.g., trial personnel, local HCPs, and trial participants) using software to support the conduct of DCTs.

- There are several ways local HCPs can submit trial-related data for inclusion in clinical trial records, including but not limited to the following:

  - If the local HCPs have access to the eCRF, they can enter trial-related data directly into the eCRFs.[48]

  - Alternatively, local HCPs can upload forms or documents by using methods of secure data transfer to investigators. Investigators or other trial personnel are then responsible for entering these trial-related data into the eCRF.[49]

- Remote trial personnel or local HCPs submitting trial data directly into the eCRF should be included in the sponsor's list of authorized data originators.[50]

- Software programs that are used to produce and process trial records required by the FD&C Act and FDA regulations are subject to 21 CFR part 11. These programs must ensure data reliability, security, privacy, and confidentiality.[51]

- FDA considers real-time video interactions, including telehealth, as a live exchange of information between trial personnel and trial participants. These live interactions are not considered electronic records and, therefore, are not subject to 21 CFR part 11, but local laws governing telehealth may apply. Privacy and security of these real-time visits should be ensured, and the visits must be documented.[52] If this documentation is captured in electronic form, such documentation is subject to 21 CFR part 11.

[48] See the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013).

[49] See 21 CFR 312.62 and 812.140.

[50] See the guidance for industry *Electronic Source Data in Clinical Investigations*. As recommended in that guidance, "[a] list of all authorized data originators (i.e., persons, systems, devices, and instruments) should be developed and maintained by the sponsor and made available at each clinical site."

[51] See 21 CFR part 11. See also the guidance for industry *Electronic Source Data in Clinical Investigations* and the revised draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* (when final, this guidance will represent FDA's current thinking on this topic).

[52] See 21 CFR 312.62(b) and 812.140(a)(3).

GLOSSARY

The following terms are defined for the purposes of this guidance:

clinical laboratory facilities: Clinical laboratories or testing facilities that contribute to or support the clinical study, such as diagnostic labs performing blood work, imaging centers, or cardiology labs. As appropriate, these clinical laboratory facilities may be located close to trial participants' homes.

data management plan (**DMP**): A written document that describes the data a sponsor expects to acquire or generate during the course of a research study; how the sponsor intends to manage, describe, analyze, and store said data; and what mechanisms will be used at the end of the study to preserve and share the research data.

decentralized clinical trial (**DCT**): A clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites.

digital health technology (**DHT**): A system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products.

investigational product (**IP**): Human drugs, biological products, or devices that are being investigated in a clinical trial.[53,54,55]

telehealth: The use of electronic information and telecommunications technologies to support and promote long-distance clinical health care.

[53] See footnote 3.

[54] See footnote 4.

[55] See footnote 5.