Conducting Clinical Trials With Decentralized Elements

Guidance for Industry, Investigators, and Other Interested Parties

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)

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Conducting Clinical Trials With Decentralized Elements Guidance for Industry, Investigators, and Other Interested Parties [1]

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

I. INTRODUCTION

This guidance provides recommendations for sponsors, investigators, and other interested parties regarding the implementation of decentralized elements in clinical trials.[2] Decentralized elements allow trial-related activities to occur remotely at locations convenient for trial participants. Decentralized elements can include, among other things, **telehealth**[3] visits with trial personnel, in-home visits with remote trial personnel, or visits with local health care providers (HCPs)[4] (see sections II and III.B). In this guidance, a **decentralized clinical trial** (**DCT**) refers to a clinical trial that includes decentralized elements where trial-related activities occur at locations other than traditional clinical trial sites.

FDA's regulatory requirements for investigations of medical products are the same for trials that

[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] This guidance is intended to apply to decentralized clinical trials (DCTs) that are required to be conducted under an investigational new drug application (IND) and are subject to the requirements under 21 CFR part 312 and to DCTs that require approval of an investigational device exemption (IDE) application under 21 CFR 812.20(a). However, the considerations in this guidance may be relevant for clinical trials that do not require an IND or an IDE application (such as investigations of "nonsignificant risk" devices conducted under 21 CFR 812.2(b)). FDA recommends that sponsors and investigators of clinical trials that do not require an IND under 21 CFR part 312 or approval of an IDE application under 21 CFR 812.20(a) take the considerations in this guidance into account when implementing decentralized elements in such trials.

[3] Terms that appear in **bold** at first mention are defined in the Glossary.

[4] For research supported or conducted by the Department of Health and Human Services and subject to the requirements under 45 CFR part 46, parties should consider the Office for Human Research Protections (OHRP) guidance *Engagement of Institutions in Human Subjects Research* (October 2008) when evaluating whether local health care-providing organizations are engaged in research. The guidance is available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html. Parties should also consider OHRP's 2009 clarification of the 2008 engagement guidance and 2011 correspondence on non-engaged scenarios, which are available, respectively, at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/determining-when-institutions-are-engaged-in-research/index.html and https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-22-2011-non-engaged-scenarios/index.html.

include decentralized elements and trials that do not include decentralized elements.[5] Section 3606(a) of the Consolidated Appropriations Act, 2023 directs FDA to issue a final guidance that includes recommendations to clarify and advance the use of DCTs to support the development of drugs and devices.[6] 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)(2) of the Consolidated Appropriations Act, 2023. The content described in section 3606(b) of Consolidated Appropriations Act, 2023 is further addressed through this guidance's reference to the guidance for industry, investigators, and other stakeholders entitled *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

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. For example, laboratory tests are often conducted by **clinical laboratory facilities** at locations remote from traditional clinical trial sites. DCTs have the potential to expand access to more representative patient populations and improve trial efficiencies.[7] Advances in using electronic communications and information technology to interact with trial participants in different locations (i.e., telehealth) allow for fewer in-person visits to traditional 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 limited access to traditional clinical trial sites. This may help improve trial participant engagement, recruitment, enrollment, and retention of a more representative trial participant population to improve the strength and generalizability of the evidence produced by the trial.

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[5] See 21 CFR parts 312 and 812.

[6] 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. 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*. See section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h)(1)) for the definition of a *device*.

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

Trials where all activities are decentralized may be appropriate for **investigational products** (**IPs**) that have well-characterized safety profiles (see section III.G) and do not require complex preparation, administration, or medical assessments. Alternatively, there may be cases when the administration of an IP or a complex medical assessment needs to be performed at a traditional clinical trial site and some follow-up assessments could be performed remotely through electronic patient-reported outcome measures, via telehealth or in-home visits, or by local HCPs, as appropriate.

Challenges related to DCTs may include coordination of trial activities with individuals and facilities in multiple locations that are not traditional clinical trial sites. Specific plans to facilitate decentralization of the trial should include, as appropriate, the use of local HCPs, local clinical laboratory facilities, and local health care facilities; visits to trial participants' homes; and direct distribution of the IP to trial participants at their locations.[8] Specific issues related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with the relevant FDA review divisions.[9,10] Appropriate training, oversight, and up-front and continuing 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 implementing decentralized elements in clinical trials.

A. DCT Design and Conduct

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, mobile research units, or local health care facilities). DCTs may involve a network of locations where trial personnel and local HCPs work and where trial-related activities (e.g., imaging and laboratory tests) are performed. Whether trial-related activities are performed by local HCPs or trial personnel, the clinical trial should be designed to

[8] See 21 CFR 312.57(a), 312.60, 312.62(a), 812.100, 812.110, 812.140(a)(2), and 812.140(b)(2) (describing requirements for IP accountability and disposition of the IP).

[9] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (August 2023). 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* (June 2023).

[10] The principles discussed in this guidance may be relevant for bioequivalence studies conducted to support abbreviated new drug applications (ANDAs). If an ANDA applicant is interested in conducting a bioequivalence study using decentralized elements, CDER's Office of Generic Drugs encourages submission of controlled correspondence or a pre-ANDA meeting request (if applicable) to discuss the design, analysis, and implementation of the study before conducting it. See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024). For submitting a pre-ANDA meeting request, see the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022).

limit variability in the data collected by including, as applicable, specific instructions in the protocol for performing these activities.

DCTs that permit tests to be performed independently by participants at home (e.g., spirometry) may introduce variability compared to tests performed under supervision at traditional clinical trial sites. Training or video supervision (i.e., during a telehealth visit) may reduce such variability. Likewise, allowing participants to choose whether an assessment will be performed at a traditional clinical trial site or remotely may result in bias (e.g., sicker participants may prefer remote visits). The protocol should specify which visits will be conducted at traditional clinical trial sites, which visits will be conducted remotely, and which visits can be left to participants' choice. In general, obtaining patient input may be helpful in ensuring that the clinical trial design fits participants' needs and that remote activities are feasible.

When designing a trial with decentralized elements, certain statistical approaches may be challenging to implement. For example, when the effect size of an active control, such as a drug indicated for sleep disorders, has been determined based upon data collected at traditional clinical trial sites, the same effect size may not be seen for the active control assessed remotely in a DCT (e.g., via telehealth or in a participant's home). This may present challenges in calculating a non-inferiority margin. Sponsors should consult with the relevant FDA review division 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. Remote clinical trial visits may include telehealth visits, participant visits to local HCPs, or in-person visits by trial personnel or local HCPs to participants' homes. The following should be considered when planning remote clinical trial visits or remote clinical trial-related activities:

- When designing a DCT, sponsors can consider telehealth visits instead of in-person visits with trial participants if no in-person interaction is needed. The sponsor should consider the IP and the medical condition of the anticipated trial population when determining whether telehealth visits are appropriate. The protocol should specify when a telehealth visit with a trial participant is appropriate and when a participant should be seen in person.

- Investigators should take measures to ensure the privacy of in-home and telehealth visits. For participants sharing their residence with others, this may involve accommodating times most suitable for participants and the possibility of using convenient locations outside of participants' homes.

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

use these local HCPs (such as doctors or nurses) to perform certain trial-related activities; for example, on a fee-for-service basis. The trial-related activities local HCPs perform should not differ from those that they are qualified to perform in clinical practice and should not require a detailed knowledge of the protocol, investigator's brochure, or IP (e.g., performing physical examinations or obtaining vital signs). These local HCPs would not be considered trial personnel, nor would they be considered subinvestigators in a drug trial.[11]

- Trial-related activities that are unique to a research study (i.e., not routine in clinical practice) and/or require a detailed knowledge of the protocol, investigator's brochure, or IP should be performed by qualified trial personnel who have been appropriately trained on the protocol. When applicable, both trial personnel and trial participants should be trained on how to conduct or participate in a telehealth visit and other visits not conducted at traditional clinical trial sites (e.g., home visits).

- Study records should indicate if a visit was conducted via telehealth and should include the date of the visit and the name of the person who conducted 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.

- Sponsors and investigators should 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 and securely from trial participants wherever they are located. The sponsor should consider the following information regarding the use of DHTs in a DCT:

- The guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* 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 evaluating drugs, biological products, and devices. The guidance discusses, among other things, selection of DHTs for use in clinical trials; verification, validation, and usability evaluations; use of DHTs to collect data for clinical trial endpoints; training on the use of DHTs; and management of risks related to the use

[11] Local HCPs can also be utilized in clinical trials that are integrated into routine clinical practice. See the draft guidance for industry *Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice* (September 2024). When final, this guidance will represent FDA's current thinking on this topic.

of DHTs in clinical trials. Other issues regarding the use of DHTs in clinical investigations are discussed in other FDA guidances.[12]

- 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 have a protocol-specified DHT are not excluded from the DCT for that reason (e.g., lower socioeconomic groups who cannot afford the DHT). Sponsor-provided telecommunication services should also be made available as needed so that participants who have no or limited access to these services are not excluded from the clinical investigation.

D. Roles and Responsibilities

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

1. The Sponsor

- Sponsor responsibilities are the same for trials that include decentralized elements and trials that do not include decentralized elements.[13] Because DCTs may involve many contracted services, sponsors should ensure proper coordination of decentralized elements (e.g., use of remote trial personnel for at-home visits, use of local HCPs, direct shipping of IP to participants) (see sections III.B and III.H). Such contracted services may be performed by networks of local HCPs (e.g., local clinic networks, pharmacy chains). Sponsors should ensure these networks of local HCPs are qualified to perform the contracted activities. Sponsors should also keep a record of these networks and other contracted service providers, including their roles and assigned activities.

[12] 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 more information on FDA's regulation of DHTs, consult the Guidances with Digital Health Content web page, available at https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content.

[13] See 21 CFR parts 312 and 812.

- The clinical trial population should reflect the intended patient population for the medical product being studied, including with respect to race, ethnicity, age, sex, and geographic location, as applicable.[14] Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of participants with diverse demographic characteristics more reflective of the intended patient population in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants who have challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may further improve engagement, recruitment, and retention of a more representative participant population and 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** or other trial-related documents:

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

  - Methods and technologies 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)[15]

  - A list identifying service providers for data collection, handling, and management

- Sponsors should describe in the trial protocol or other trial-related documents 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

  - Activities to be performed by trial personnel and those that may be performed by local HCPs

[14] See the draft guidance for industry *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (June 2024). When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* and the guidance for industry and FDA staff *Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies* (September 2017).

[15] See the revised draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* and the 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.

- Transmission of reports on activities performed at different locations (e.g., medical imaging; clinical laboratory tests; and procedures performed at trial participants' homes, work, or other local facilities)

- Delivery of IPs to trial participants, if applicable, and accountability for IPs

- Safety monitoring and management of adverse events

- Study records should capture the visit type (i.e., telehealth or in person), the visit location (e.g., participant's home, local health care facility, traditional clinical trial site), the date of the visit, and the data originator.[16]

- Sponsors should ensure compliance with local laws, regulations, and licensing requirements governing medical practice and IP administration relevant to the conduct of a DCT. This may involve addressing laws in multiple U.S. States, territories, and other countries.

- Sponsors must ensure proper monitoring of an investigation.[17] 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.[18] 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 decentralized elements. FDA recommends risk-based monitoring approaches and the 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 for protecting the rights, safety, and welfare of subjects under their care.[19] Investigators must also maintain accurate records of each subject's case history, including observations and other data pertinent to the investigation.[20] Consistent with these responsibilities, investigators should review data from other trial personnel and local HCPs, as applicable, and follow up on any data that are missing, concerning, or appear to be in error. Investigators must also ensure assessments are being completed consistent with

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

[17] See 21 CFR 312.50, 312.56(a), 812.40, and 812.46.

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

[19] See 21 CFR 312.60, 812.3(i), and 812.100.

[20] 21 CFR 312.62 and 812.140(a)(3).

the protocol[21] and confirm that participants have received the IP.[22] When permitted by the protocol,[23] investigators can delegate trial-related activities to appropriate local HCPs. Investigators can work with enrolled participants to identify such providers when appropriate. Investigators must ensure that trial-related activities delegated to local HCPs are conducted according to the investigational plan and applicable regulations and remain responsible for the adequate supervision of those to whom they have delegated these activities.[24,25]

The extent of decentralization in a clinical trial may vary depending on the investigator's use of telehealth, trial personnel working remotely, local HCPs, and/or DHTs. Whether all activities can be decentralized depends on the types of assessments and procedures needed to collect endpoints and monitor safety. Additional training, coordination, and standard operating procedures may be needed for decentralized elements to ensure consistent implementation.

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

- As part of the requirement that investigators protect the safety of subjects,[27] investigators should evaluate reports from local HCPs of abnormal signs or symptoms detected at in-person visits. Investigators should follow up with participants as appropriate.

- Videoconferencing 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 required to be conducted under an investigational new drug application (IND) under 21 CFR part 312, Form FDA 1572 must be completed by all investigators.[28] The decision to include individuals as subinvestigators in a DCT should

[21] 21 CFR 312.60 and 812.100.

[22] 21 CFR 312.61, 812.100, and 812.110(c).

[23] 21 CFR 312.60 and 812.100.

[24] Ibid.

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

[26] 21 CFR 312.60 and 812.100.

[27] See 21 CFR 312.60 and 812.100.

[28] 21 CFR 312.53(c).

be based on their assigned responsibilities. When trial personnel contribute directly and significantly to the trial data (e.g., assessing adverse events, performing a clinical outcome assessment, applying a protocol-defined scoring system) or require a detailed knowledge of the protocol, investigator's brochure, or IP, they should be included on Form FDA 1572 as subinvestigators.[29] Individuals who are not subinvestigators should not be listed on Form FDA 1572. In addition, as part of the IND, sponsors must submit a list of all investigators and subinvestigators.[30]

- Investigators do not need to maintain a log of local HCPs performing trial-related activities. However, as part of preparing and maintaining adequate case histories, investigators should ensure that reports from local HCPs include the name of the local HCP and the date when activities were performed.[31]

- For device investigations, investigator and sponsor 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 investigational device exemption (IDE) application (see 21 CFR 812.20(b)(4) and (b)(5) and 812.150(b)(4)). Local HCPs who provide trial-related services that are part of routine clinical practice and where a detailed knowledge of the protocol or IP is not required are not considered investigators and should not be included in the IDE list of investigators.

- Investigators should communicate any specific instructions included in the protocol to local HCPs for trial-related activities they are delegated to perform (e.g., having participants rest for 5 minutes before measuring a blood pressure) to limit variability and to ensure consistency and completeness of the data. Investigators should also review data provided by local HCPs regularly to ensure data quality.

- Some trial protocols will include designated clinical laboratory facilities[32] to perform activities required by the protocol (e.g., phlebotomy, x-rays). Other trial protocols may permit the use of a variety of clinical laboratory facilities close to the trial participant to perform these activities. Use of local clinical laboratory facilities is generally appropriate for routine clinical tests that are well standardized. Designated clinical laboratory

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[29] See 21 CFR 312.3(b) and 312.53(c)(1)(viii) (for a definition of *subinvestigator* and a more detailed discussion of the list of names of subinvestigators who must be included in Form FDA 1572). 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 Study Subjects*.

[30] See 21 CFR 312.23(a)(6)(iii)(b).

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

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

facilities should be used for tests that are specialized or specific to the trial. If appropriate, specimens from trial participants (e.g., blood, sputum) may be collected by remote trial personnel, local HCPs, local clinical laboratory facilities, or participants using home collection kits and sent to designated clinical laboratory facilities for processing.

- For drug trials required to be conducted under an IND, all clinical laboratory facilities must be listed on Form FDA 1572.[33] For device trials, clinical laboratories should be identified in the investigational plan as appropriate (e.g., specifying clinical laboratories that are traditional clinical trial sites in in vitro diagnostic device studies,[34] identifying use of core labs for performing critical tests, outlining plans to use local labs not associated with traditional clinical trial sites). The investigator should maintain a record of any clinical laboratory facilities used by participants under their supervision that are added during the course of either a drug or device trial. If a network of clinical laboratories is used, the name and address of the network headquarters may be listed instead of individual satellite clinical laboratories.

- As in any 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 obtain reports from these local health care facilities.

E. FDA Oversight

FDA uses a variety of tools to conduct oversight of regulated entities (e.g., sponsors and clinical investigators). This includes inspections conducted under sections 704(a)(1) or 704(a)(5) of the FD&C Act[35] and, when appropriate, remote regulatory assessments.[36] For FDA inspections of clinical investigators, the investigator should identify a physical location where a responsible person is available to facilitate the FDA inspectors' access to trial-related records (either paper or electronic access) for participants under the clinical investigator's care and to facilitate interviews with trial personnel (either in person or remotely). For INDs, the investigators

[33] See 21 CFR 312.53(c)(iv).

[34] For certain device studies, information on the clinical laboratory may need to be included in the IDE application. See, e.g., 21 CFR 812.20(b)(1), (b)(3), (b)(6), and (b)(7). For example, for some in vitro diagnostic studies, a clinical laboratory may be the sponsor of the study or a traditional clinical trial site at which the investigator is located.

[35] Generally, an inspection, such as described in section 704(a)(1) of the FD&C Act (21 U.S.C. 374(a)(1)), involves duly designated officers or employees of the FDA physically entering (at reasonable times and in a reasonable manner) establishments subject to regulation under the FD&C Act to determine compliance with applicable requirements. See section 704(a)(1) of the FD&C Act; see also FDA's Investigations Operations Manual, Section 2.2.3, Authority to Inspect (2024).

[36] See section 704(a)(4) of the FD&C Act. See also the draft guidance for industry *Conducting Remote Regulatory Assessments: Questions and Answers* (January 2024). When final, this guidance will represent FDA's current thinking on this topic.

generally identify the inspection location for clinical investigators as the address entered under sections 1 or 3 on Form FDA 1572; however, other physical locations may be identified for inspection purposes. For IDE applications, the inspection location for clinical investigators is generally included in the IDE application; however, other physical locations may be identified for inspection purposes.

F. 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.[37]

- Investigators may obtain informed consent (either electronically or on paper) from trial participants at their remote locations provided that all applicable regulatory requirements are met.[38] The process of obtaining informed consent from participants at their remote locations can include a remote visit. Obtaining informed consent is an investigator responsibility.[39] If the investigator delegates this responsibility, the individual obtaining informed consent should, among other things, have a detailed knowledge of the protocol and have the appropriate training and credentials to be able to address any questions or concerns the subject may have about the trial.[40] FDA therefore does not consider obtaining informed consent to be an appropriate activity for a local HCP to perform.

- With a DCT, the informed consent process must include notifying participants (or their legally authorized representatives) 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 in accordance with 21 CFR part 50.[41]

- When appropriate, 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.[42]

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[37] 21 CFR 56.109, 56.111, 312.66, and 812.42.

[38] 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). See also the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023).

[39] 21 CFR 50.20, 312.60, and 812.100.

[40] For additional discussion about delegation of the consent discussion, see the guidance for IRBs, clinical investigators, and sponsors *Informed Consent*.

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

[42] 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).

- As applicable, the informed consent process should inform trial participants:
  - Whether local HCPs will be used in the conduct of the trial
  - Which trial activities will take place at their homes
  - Who will have access to their protected health information

G. Investigational Products in a DCT

1. Drugs and Biological Products

The administration of an IP to participants must be performed under the supervision of the investigator or subinvestigator responsible to the investigator.[43] The investigator shall not supply the investigational drug to any person not authorized to receive the IP.[44] Sponsors should consider the nature of the IP when determining whether administration outside of a traditional clinical trial site in a DCT is appropriate. Administration of IP that has a high-risk safety profile, especially in the immediate post-administration period; that is in early stages of development such that the safety profile is not well defined; or that requires complex preparation, administration, or medical assessments may need in-person supervision by the investigator at a traditional clinical trial site. Alternatively, it may be appropriate for local HCPs or trial personnel working remotely to administer an IP at, for example, local health care facilities, mobile research units, or participants' homes if the safety profile of the IP is well characterized and specialized monitoring during the immediate period following administration is not needed.[45]

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 underlying condition in the population being studied. 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 good stability profiles. Drugs that involve specialized handling, shipping, and storage conditions may not be suited for direct shipment to locations outside the traditional clinical trial site.

[43] 21 CFR 312.61.

[44] Ibid.

[45] The same considerations may apply to administration of the control as part of the clinical trial.

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 the potential risks of the device for participants.

Investigational devices intended for home use may be appropriate for use by trial participants without the investigator's direct oversight when such direct oversight is not needed to mitigate potential serious risks to trial participants. Investigational devices that are not intended for self-use (i.e., devices used in hospital or ambulatory care settings) 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.[46] Certain follow-up assessments or procedures needed after using the investigational 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 if there are plans in place to ensure that adverse events identified during such visits will be properly assessed, managed, and documented.

H. Packaging and Shipping of Investigational Products

In some cases, DCTs may involve the direct distribution of IPs to trial participants or local HCPs. In these cases, investigators must remain responsible for supervising the supply of IP to trial participants or local HCPs.[47] When applicable, trial personnel should be trained on procedures and appropriate documentation for handling, packaging, shipping, and tracking IPs. When IPs are directly distributed to trial participants or local HCPs, such as through a central distribution service, the investigator must authorize the release of the IP by the distributor; ensure receipt by trial participants or local HCPs, which should be done according to procedures described in the investigational plan or other trial-related documents; and document the return or disposal of any unused product as directed by the sponsor.[48] When IPs are shipped directly to participants, investigators should ensure participants have appropriate instructions for use of the product.

Sponsors should address the following in trial-related documents:

- How the physical integrity and stability of the IP will be maintained during shipment, including appropriate packaging materials and methods (e.g., temperature control).

[46] See 21 CFR 812.110.

[47] See 21 CFR 312.61 and 812.110.

[48] See 21 CFR 312.59, 312.60, 312.61, 312.62(a), 812.100, 812.110(c) and (e), and 812.140(a)(2).

Shipping containers should include clear instructions for recipients who are handling and storing IPs and instructions for returning unused IPs.[49,50]

- How investigators will track and document receipt of IPs by participants or local HCPs.

- How unused IPs will be returned to the sponsor or disposed of and how this will be documented.[51]

I. Safety Monitoring in DCTs

To protect the safety and welfare of trial participants in a DCT, sponsors should implement a safety monitoring plan that addresses the following:

- The safety monitoring plan should take the decentralized nature of the clinical trial into account and ensure that adverse events and medication errors are appropriately collected and adequately addressed.[52] Generally, adverse events should be captured during scheduled visits with investigators or trial personnel. However, there may be instances when local HCPs performing trial-related activities become aware of a concerning sign, symptom, or clinical event. The safety monitoring plan should describe how local HCPs will be instructed to report such findings.

- As in any 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.[53]

- When applicable, the safety monitoring plan should describe the type of information that will be collected by a DHT, how that information will be used and monitored, and what

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

[50] 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).

[51] See 21 CFR 312.59, 812.110(e), 812.140(a)(2), and 812.140(b)(2) (for requirements related to disposition of the IP).

[52] 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).

[53] For information about the medical care of trial participants, see section 2.7.1 in the ICH draft guidance for industry *E6(R3) Good Clinical Practice (GCP)* (June 2023). When final, this guidance will represent FDA's current thinking on this topic.

action trial participants or personnel should take in response to abnormal findings or electronic alerts.[54]

Trial participants should have clear instructions about how to contact trial personnel to report adverse events and to have pertinent questions answered. Trial participants should also be able to arrange for an unscheduled visit with trial personnel using telehealth or an in-person visit, as appropriate (see section III.B).

If unreasonable and significant safety risks emerge because of use of an IP (e.g., due to remote administration), sponsors must discontinue all or part of the trial presenting the risk (e.g., discontinue remote administration or use) and notify FDA, the IRB, and all investigators who have participated in the trial.[55]

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 tests and review them in a timely manner.

J. Electronic Systems Used When Conducting DCTs

- Electronic systems 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 trial activities
  - Tracking IPs that are shipped directly to trial participants
  - Syncing information recorded by DHTs
  - Serving as communication tools between trial personnel and trial participants

[54] For more information on safety monitoring as it relates to DHTs used in clinical investigations, see the guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*.

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

- Training should be provided to all parties (e.g., trial personnel, local HCPs, and trial participants) who are using electronic systems 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:

  - An eCRF can be designed to allow local HCPs to enter trial-related data directly into the eCRF.[56]

  - Local HCPs can send forms or documents electronically by methods of secure data transfer (e.g., via secure email or fax) to investigators who are responsible for entering these trial-related data into the eCRF and retaining the trial-related records.[57]

- 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.[58]

- Electronic systems 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.[59] These systems must ensure data reliability, security, privacy, and confidentiality.[60]

- FDA considers real-time video and audio interactions 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 other requirements governing telehealth, including local laws, may apply. However, the visits must be documented (e.g., visit notes),[61] and if such documents are in electronic form, they must be captured in systems that are subject to the requirements in 21 CFR part 11.[62] Investigators should ensure the privacy and security of these real-time visits.

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[56] See the guidance for industry *Electronic Source Data in Clinical Investigations*.

[57] See 21 CFR 312.62 and 812.140(a).

[58] 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."

[59] See 21 CFR 11.1.

[60] 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*.

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

[62] See 21 CFR 11.1(b).

GLOSSARY

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

clinical laboratory facilities: Clinical laboratories or other testing facilities directly contributing to or supporting the clinical trial (e.g., diagnostic labs performing blood tests, imaging centers, cardiology labs).

data management plan: A written document that describes what data a sponsor expects to acquire or generate during the course of a clinical trial; 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 that includes decentralized elements where 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.[63]

telehealth: The use of electronic information and telecommunications technologies to support remote interactions between clinical trial personnel and trial participants.

[63] See 21 CFR 312.3(b) and 812.3(g).