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ALERT

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FDA Guidance Clarifies Approach to Decentralized Clinical Trials

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On May 2, 2023, FDA issued a draft guidance document providing insights into the Agency's approach to regulating decentralized clinical trials ("DCTs") for drugs, biological products, and devices ("DCT Draft Guidance"). The DCT Draft Guidance builds on Agency recommendations issued beginning in March 2020 to facilitate trial decentralization in response to the COVID-19 pandemic and associated clinical trial disruptions such as quarantines, site closures, and travel limitations. As part of the Food and Drug Omnibus Reform Act ("FDORA"), enacted in late 2022, FDA was required to "issue or revise draft guidance that includes recommendations to clarify and advance the use of decentralized clinical studies to support the development of drugs and devices"—a requirement that is addressed by the DCT Draft Guidance.

As a general matter, FDA's regulatory requirements for DCTs are the same as those for traditional site-based clinical trials.[1] However, DCTs can also present unique challenges. The DCT Draft Guidance provides various recommendations regarding how sponsors, investigators, and other stakeholders can satisfy regulatory obligations in the context of DCTs and advance the use of such studies in the future. This effort is particularly important because of the numerous advantages that DCTs can provide, including the potential to enhance convenience for trial participants, reduce the burden on caregivers, expand access to more diverse populations,[2] improve trial efficiencies and facilitate research on rare diseases and diseases affecting populations with limited mobility.[3,4] The issuance of the DCT Draft Guidance is a demonstration of FDA's commitment to modernizing its approach to regulating clinical research to help achieve these important ends. It is also an example of how certain innovations driven or accelerated by the COVID-19 pandemic may have long-lasting benefits.

Background

DCTs are clinical trials where some or all of the trial-related activities occur at locations other than traditional clinical trial sites, such as trial participants' homes or local health care facilities that are convenient for trial participants. The term encompasses both fully decentralized trials, in which all activities take place at locations other than traditional trial sites, as well as hybrid DCTs in which only some trial activities occur in nontraditional settings.

While the movement toward DCTs predates COVID-19 largely due to the emergence of increasingly reliable technologies for capturing patient data outside of traditional health care settings, the onset of the pandemic significantly accelerated this trend. Because the requirements for DCTs are the same as those for traditional site-based clinical trials, the DCT Draft Guidance relies heavily on concepts described in prior FDA guidances, including those addressing digital health technologies, risk-based approaches to study monitoring, electronic informed consent, electronic data capture, and more.

Key Developments

The DCT Draft Guidance focuses on various specific topics related to DCT implementation, including:

- **DCT Design.**
    - Central Trial Site. The DCT Draft Guidance states that while DCTs, by definition, involve at least some of the trial-related activities occurring away from a traditional trial site, DCTs should still have a central physical location where all clinical trial-related records for participants are accessible for inspection and where trial personnel can be interviewed.

- Non-Inferiority Trials. The variability and precision of the data obtained in a DCT may differ from that obtained in a traditional site-based clinical trial. While this would not affect a finding of superiority in a clinical trial, the DCT Draft Guidance states that it may affect the validity of a finding of non-inferiority and may present challenges in calculating a non-inferiority margin. As a result, the draft guidance recommends that sponsors consult FDA review divisions when planning a non-inferiority trial in a DCT setting.

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

  - Telehealth Visits. The DCT Draft Guidance states that telehealth visits may be used instead of in-person visits if no in-person interaction is needed; the protocol should specify when a telehealth visit is appropriate and when participants should be seen in person. The protocol should also specify how adverse events identified remotely will be evaluated and managed. Telehealth visits should otherwise be completed in accordance with typical clinical trial and telehealth laws, regulations, and requirements, which in the United States will frequently require close attention to health care provider licensure requirements in the states in which trial subjects are located.

  - Appropriate Personnel. The DCT Draft Guidance states that, while in-person visits and trial-related activities should generally be conducted by trial personnel, they may also be conducted by health care professionals ("HCPs") who are not otherwise part of the trial if the services being provided (i) do not differ from those that the HCP is qualified to perform in clinical practice, and (ii) do not require a detailed knowledge of the protocol or the investigational product. Any activities that are unique to the research or require specific knowledge of the protocol or the investigational product should be performed by qualified trial personnel who have been appropriately trained.

- **Use of Digital Health Technologies for Data Transmission.** The DCT Draft Guidance identifies various other resources and documents that provide relevant recommendations for obtaining data remotely using digital health technologies. These resources include FDA's guidances on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers; and Clinical Decision Support Software; as well as the BEST (Biomarkers, EndpointS, and other Tools) Resource discussing patient-reported outcomes and other clinical outcome assessments. The DCT Draft Guidance states that sponsors should ensure that digital health technologies are available and suitable for use to all trial participants, and that when personal digital health technologies are permitted during a DCT, sponsor-provided technologies should be made available to ensure that participants who do not have or cannot afford such technology are not excluded from the trial for that reason. While not discussed in the DCT Draft Guidance because it falls outside the scope of FDA's authority, the provision of such technologies by trial sponsors must be evaluated carefully for compliance with fraud and abuse laws, such as the Anti-Kickback Statute and Civil Monetary Penalty Law Beneficiary Inducement provisions.[5]

- **Roles and Responsibilities of Sponsors and Investigators.**

  - Sponsors. FDA underscores that sponsor responsibilities are the same for DCTs and traditional site-based clinical trials. However, because DCTs may involve many contracted services (e.g., use of local HCPs, shipping services), sponsors should take care to ensure proper coordination of the decentralized activities.

- The DCT Draft Guidance states that sponsors should strive for diversity and inclusiveness in trial populations,[6] and it is clear that FDA considers this to be one of the material advantages of DCTs.

- The DCT Draft Guidance offers additional insights into information that should be included in the data management plan, trial protocol, case reports, and trial monitoring plan to address the specific context of a DCT.

- Sponsors must comply with all relevant local laws, regulations, and licensing requirements, including those governing medical practice and administration of investigational products when conducting a DCT. This may require consideration of laws and regulations across multiple states, territories, or countries, as applicable.

  - Investigators. A key difference in the role of an investigator in a DCT as compared to a traditional site-based trial is the extent to which the investigator uses telehealth for remote study visits and other study activities, contracts with local sub-investigators to provide trial-related services, and employs digital health technologies to capture or record patient data or outcomes. Such decentralized features may necessitate additional training, coordination, and standard operating procedures to ensure consistent implementation. The DCT Draft Guidance provides specific examples of how investigators may need to adjust their various roles and activities to account for the decentralized nature of a DCT.

- **Informed Consent and IRB Oversight.** Informed consent may be obtained remotely as part of a DCT, and the DCT Draft Guidance provides additional clarity on this process. Additionally, IRB oversight is required for DCTs, and the DCT Draft Guidance recommends the use of a central IRB to facilitate efficient review of the protocol and other relevant information and documentation.

- **Use and Administration of Investigational Products.**

  - Drugs and Biological Products. FDA regulations require that investigational drugs be administered to participants only under a study investigator's personal supervision or the supervision of a sub-investigator responsible to the investigator. In the DCT Draft Guidance, FDA provides recommendations on how an investigator should evaluate the complexity of administration method, risk and safety profile, and development stage of the product when determining whether administration may occur at a location other than a clinical trial site.

  - Medical Devices. The appropriate use and administration of an investigational device depends on the device's intended use, instructions for use, and level of risk. Whereas medical devices for home use that do not pose significant risks to trial participants may be appropriate for use by participants without direct oversight by the investigator, 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 only be used or administered by qualified trial personnel with investigator oversight. The DCT Draft Guidance provides FDA's thinking regarding appropriate contexts for follow-up procedures needed after administration of the investigational device.

- **Packaging and Shipping of Investigational Products.** Generally, DCTs may allow for the direct distribution of investigational products to trial participants at their locations, though this process—as well as the return and disposal of unused product—should be controlled and monitored by the DCT investigator according to procedures described in the protocol. The DCT Draft Guidance provides recommendations regarding packaging,

shipping, and storage of the investigational products, including guidance regarding the information to be included in the protocol and packaging materials, and the training of DCT personnel regarding handling, packaging, shipping, tracking, and documentation procedures.

- **Implementation of a Safety Monitoring Plan.** DCT sponsors, like sponsors of traditional trials, are required to ensure proper monitoring of the investigations and that investigations are conducted in accordance with the investigational plan and protocols. In a DCT, sponsors should implement a safety monitoring plan that takes the decentralized nature of the trial into account. The DCT Draft Guidance provides insights into specific elements that should be included in the safety monitoring plan and considerations for reporting including, but not limited to, descriptions of how participants are expected to respond to and report adverse events, and of the type of information that will be collected by digital health technologies, 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 investigational product, sponsors must discontinue such remote administration or use, notify relevant parties (including FDA, the IRB, and all participating study investigators), and determine whether the trial should continue, as required by FDA's generally applicable clinical trial regulations.
- **Software Used in Conducting DCTs.** Software for various functions can be used to support the conduct of DCTs including, but not limited to, software to manage electronic informed consent, software to manage electronic case report forms, software to schedule trial visits and other DCT-related activities, and software serving as a communication tool between DCT personnel and trial participants. All software programs used in DCTs must comply with applicable laws and regulations including, but not necessarily limited to, 21 CFR Part 11, as well as laws governing privacy, security, and telehealth, as applicable. The DCT Draft Guidance states that FDA considers real-time video interactions, including telehealth interactions, as live exchanges of information between trial personnel and participants that are not considered electronic records, and therefore are not subject to 21 CFR Part 11. However, if documentation of the visits is captured in electronic form, such documentation would be subject to Part 11. Regardless, local laws governing telehealth and medical practice may apply to these visits.

Next Steps

In addition to the DCT Draft Guidance, FDA has been working on various other resources for DCT sponsors, patients, and HCPs to better understand the role of DCTs and digital health technologies in drug, biological product, and medical device development. FDA has explicitly encouraged sponsors of applications or other stakeholders who are considering innovative approaches to clinical trials, including DCTs, to reach out to FDA directly as early as possible.[7] Additionally, FDA has established a steering committee aimed at providing advice on, among other things, the implementation of DCTs not associated with a specific drug development program.[8] While there is more to do, the DCT Draft Guidance is a meaningful step to help stakeholders understand how DCTs may continue to play an integral role in product development. It also signals FDA's willingness to modernize in the area of clinical trials and emphasizes FDA's ongoing commitment to expanding access to more diverse populations for clinical research, improving trial efficiency, and facilitating research on rare diseases and diseases affecting populations with limited mobility.

Comments on the draft guidance are due on August 1, 2023. Ropes & Gray will continue to monitor developments in the area. If you have any questions, please contact any member of our FDA regulatory practice or your usual Ropes & Gray advisor.

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1. *See* 21 CFR Parts 312 and 812.

2. Promoting diversity in clinical trial enrollment is another key component of FDORA, which requires FDA to issue additional guidance on diversity action plans in clinical trials by late December 2023. For more information on FDORA's provisions promoting diversity in clinical trial enrollment, see our earlier Ropes & Gray alert available here: https://www.ropesgray.com/en/newsroom/alerts/2023/01/congress-enacts-legislation-requiring-guidance-on-clinical-research-diversity-and-modernization.
3. *See, e.g.,* FDA, Press Release: "FDA Takes Additional Steps to Advance Decentralized Clinical Trials," *available at* https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials.
4. *See, e.g.,* FDA, "Guidance for Industry: Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs," *available at* https://www.fda.gov/media/127712/download.
5. *See* 42 U.S.C. 1320a-7b(b), 42 U.S.C. 1320a-7a(a)(5).
6. *See* FDA, "Draft Guidance for Industry: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials," *available at* https://www.fda.gov/media/157635/download.
7. *See* FDA, "Stakeholder Engagement with FDA," *available at* https://www.fda.gov/science-research/science-and-research-special-topics/stakeholder-engagement-fda.
8. *See* FDA, "CDER Conversation: The Evolving Role of Decentralized Clinical Trials and Digital Health Technologies," *available at* https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-evolving-role-decentralized-clinical-trials-and-digital-health-technologies.