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Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted at <https://www.regulations.gov/docket/FDA-2022-D-2870>

Re: Docket No. FDA-2022-D-2870

Decentralized Clinical Trials for Drugs, Biological Products, and Devices:
Draft Guidance for Industry, Investigators, and Other Stakeholders

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the request of the Food and Drug Administration (FDA) for comments on the draft “*Decentralized Clinical Trials for Drugs, Biological Products, and Devices: Draft Guidance for Industry, Investigators, and Other Stakeholders*”, published in the Federal Register on May 1, 2023. It is a timely, welcome, and important draft guidance.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.¹

The MRCT Center applauds FDA’s considerations of the benefits and challenges of decentralized clinical trials (DCTs), and thanks FDA for offering recommendations in the guidance document on fully decentralized clinical trials as well as hybrid trials that combine in-person visits with activities beyond the clinical trial site (local imaging, laboratory or healthcare facility, the participant’s home, etc.). The guidance acknowledges the increased use of DCT methods and their advantages (e.g., increased access to trials, potential greater trial efficiencies) and emphasizes that the core regulatory requirements for clinical trials do not differ between tradition trials and DCTs. We also appreciate the consideration of the important role of health

¹ Brigham and Women’s Hospital, Mass General Brigham, Ropes and Gray LLP, Harvard Medical School, and Harvard University.

care providers (HCPs) whose activities and responsibilities are considered in the guidance. The MRCT Center appreciates and fully supports the recommendations made, and we comment here to propose some further clarifications that would be welcome.

IIIA. DCT Design

1. The guidance states that “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.” We suggest that FDA clarify that electronic records, in addition to paper records and physical source documents, are included in the definition of “clinical-trial related records.” In addition, the guidance should specifically state that trial personnel can be interviewed remotely through a web-enabled platform.
2. We agree that “the variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial.” (Lines 98-99) Further guidance on the statistical implications of the variability and precision of data, in addition to the concern of a non-inferiority design, would be welcome, as would ways to mitigate variability and precision.

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

1. While there are many excellent recommendations on the conduct of remote visits and trial-related activities, there are also a number of clarifications of those recommendations that would be helpful.
 - a. Line 118-121. Guidance on the factors that would determine whether in-person visits are necessary or telehealth visits are possible would be helpful. It would be helpful to note whether, in addition to the investigator’s making this determination, the sponsor could also recommend whether in person visits are necessary or telehealth visits are possible. (This is particularly relevant because the protocol is often written by the sponsor, then reviewed by the investigator.) Is the term “telehealth visits” synonymous with “remote visits?” Additionally, how much information and detail on these remote methods must be specified in the protocol submitted to the IRB?
 - b. Line 126ff. The role of the HCP requires further clarification, as the differentiation of HCPs from sub-investigators (who are identified on the Form FDA 1572) and investigators (who sign a Form FDA 1572) remains unclear. For these purposes, how does one differentiate an HCP from a sub-investigator or an investigator? What does “a detailed knowledge of the protocol or IP” mean? If the HCP is providing trial data (e.g., a vital sign collected as standard of care but is intended to be used as an endpoint in the trial), is that HCP automatically considered an investigator? If the HCP obtains specimens (e.g., blood draw) from

a participant the results of which will “contribute directly and significantly to the trial data,” is the HCP now considered an investigator? If the provider manages the IP, even if intimately familiar with the IP (e.g., an approved, marketed product now studied in a de-escalation trial or in a new indication), is the provider considered to be an investigator? If so, who is then responsible for documentation of administration, monitoring, and product accountability?

- c. During the June 20, 2023, Town Hall that FDA gave on the draft guidance there were several questions about the extent to which the investigator needs to supervise HCPs. We understood FDA to respond that investigators would not necessarily be expected to provide direct or significant oversight over local HCPs’ performance of activities within their routine clinical practice and that oversight and monitoring in such instances may merely require that investigators ensure that such personnel are appropriately qualified for the delegated clinical trial-related activities and regularly review reports they submit for timeliness and quality. It would be helpful if these observations from the Town Hall could be incorporated into the draft guidance along with an explanation of what the limits of the HCP’s responsibilities should be and how the investigator should qualify the delegated responsibilities (other than reviewing a CV/resume and credentialing) given that this information is not required on the Task Log.
- d. Lines 369-375 of the guidance suggest that an investigator or sub-investigator must always administer the IP; however, lines 377-382 introduce the possibility of an HCP administering an IP. Further clarity on when an IP may be administered by an HCP would help sponsors and investigators to understand the permissible roles of HCPs in this context. For example, if an HCP is geographically distant from the PI, does there also need to be a local investigator in order for the HCP to administer the IP? Geographic distance² appears to be one of the factors in traditional clinical trials that determines whether trial personnel can function as a sub-investigator (e.g., delegated responsibilities on the Form FDA 1572) or should be listed as an investigator completing a Form FDA 1572.
- e. A related question is how an investigator may exercise adequate supervision of an HCP whose activities rise to the level of being a sub-investigator listed on the Form FDA 1572, if the HCP is employed by a service provider contracted by the

² See FAQ #21 at <https://www.fda.gov/media/78830/download> “In some situations, it is preferable to have more than one investigator responsible for a clinical investigation. For example, when a study is conducted at multiple research facilities that are not in close proximity, FDA expects an investigator who has signed a 1572 to be available at each location to either personally conduct or supervise the study. This responsibility cannot be delegated to a subinvestigator.”

sponsor. The guidance document does not address the reality that these types of service providers are often contracted directly by the study sponsor to provide services nationwide for subjects who may be enrolled at numerous study sites, each with its own investigator. The investigator and his or her institution often lack privity of contract with the vendors furnishing the required services, and thus take the position that they are not able to exercise supervision over the vendors and the vendor's staff members. Further clarity from FDA in the final guidance regarding how appropriate oversight can be provided in instances in which the investigator and sub-investigators are employed by different entities would be helpful to support the expansion of DCTs in instances in which a nationwide service contracted by the sponsor provides clinical services to study subjects located at multiple sites.

- f. Line 140. "During each remote trial visit, investigators should confirm the trial participant's identity." It seems reasonable to include an HCP as a person able to confirm the trial participant's identity if that HCP is performing the remote trial visit. We recommend that Line 140 be modified to include HCPs and other responsible personnel.

IIIC. Digital Health Technologies

1. We appreciate that FDA has specifically recommended provision of DHTs if a participant does not have or cannot afford them. The guidance should acknowledge that, in addition to sponsors, sites and/or investigators may also provide DHTs. In addition, we recommend FDA mention that (1) technical assistance for the use of DHTs should be provided, (2) loss of or damage to the DHT should not result in penalties or adverse actions (e.g., financial penalties, removal from the study), (3) the capacity to access the device remotely and wipe all research data in the event of device loss is expected, (4) the disposition of the DHT at the end of trial (e.g., an expectation of return, gifted to the participant) should be specified, (5) a plan for data breach should be in place, and (5) data access plans and other ancillary costs in a DCT are reimbursable expenses for the participant.
2. FDA should note the challenges of privacy, confidentiality, and security when using DHTs and provide recommendations to mitigate risks. We encourage FDA to coordinate on this issue with the U.S. Department of Health and Human Services ("HHS") Office for Civil Rights ("OCR"), which has in the past year issued guidance and warnings to health care providers regarding online tracking technologies present in many DHTs.³

³ See OCR, Use of Online Tracking Technologies by HIPAA Covered Entities and Business Associates, <https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/hipaa-online-tracking/index.html> (December 2, 2022); see also Federal Trade Commission, FTC and HHS Warn Hospital Systems and Telehealth Providers about Privacy and Security Risks from Online Tracking Technologies,

3. The recommendation that DHTs be provided for free by sponsors or investigators to trial subjects potentially implicates federal fraud and abuse laws, including the Anti-Kickback Statute (“AKS”) and the Civil Monetary Penalty Statute beneficiary inducement provisions (“CMP”), when such subjects are federal health care program beneficiaries.⁴ Concerns about violating these laws may make sponsors and investigators hesitant to provide DHTs during clinical trials. We encourage FDA to work with the HHS Office of Inspector General to consider guidance on how DHTs may be provided to clinical trial subjects without the sponsor, investigator or research site violating the AKS and CMP.

IIID. Roles and Responsibilities

1. Operational aspects of the DCT are stated as the sponsors’ responsibility (i.e., scheduled and unscheduled, remote or in-person clinical trial visits, report transmission, shipment and accountability for IP, safety monitoring, and responding to adverse events). How then can the investigator be responsible for the conduct of the study? Accountability should follow the authority and responsibility for any task. It would be helpful for FDA to clarify its thinking on this.
2. The sponsor contracts the third-party vendor, but the investigator is responsible for vendor conduct. What is the role and/or authority of investigators in the event of non- or poor performance of third-party vendors when the contract exists between the sponsor and vendor? Does the investigator have any redress, and is the investigator required to act?
3. There is no section or specific mention of sponsor-investigators in the section on roles and responsibilities. Any differences in responsibilities when the roles of sponsor and investigator are fused would be helpful to annotate.
4. The draft guidance states, “[a]ll clinical laboratory facilities should be listed on Form FDA 1572.” This is often impractical, since the local clinical laboratory (or other site for research procedures such as imaging) is not known until the participant has been identified and/or enrolled. Therefore, further clarity would be helpful. Is it sufficient to list a third-party (e.g., Quest Diagnostics, Shields Imaging, Walgreens) and assume that these entities are responsible for validating and providing oversight to each of their sites, or must each physical facility be listed independently? Can the protocol describe the qualifications of an acceptable facility (e.g., licensed CLIA-approved laboratory) or must

<https://www.ftc.gov/news-events/news/press-releases/2023/07/ftc-hhs-warn-hospital-systems-telehealth-providers-about-privacy-security-risks-online-tracking> (July 20, 2023).

⁴ 42 U.S.C. § 1320a-7b(b); 42 U.S.C. § 1320a-7a(a)(5).

each facility be listed? We are conscious of the administrative burden this may place on the investigator.

Minor suggestions:

1. In the introduction, it would be helpful to identify additional challenges in DCTs, including privacy and confidentiality, third party risks, security, data management, and, in addition to access to digital health technologies (DHTs) for remote data acquisition themselves, comfort and ease of use of DHTs and access to the internet. The introduction of DCTs in this context should not create new underrepresented populations such as older individuals or those living in digitally remote areas. This annotation in the introduction, we suggest, would be additional to the considerations in the section on DHTs.
2. Also in the introduction, lines 73-76, state: “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.” We suggest that the list of alternate sites/facilities should either be more complete (e.g., local imaging facilities, local pharmacies) or be listed as exemplary.
3. Lines 109-110 state, “The FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting.” While trivial, we would suggest that the FDA review divisions be consulted whenever a trial, and particularly a DCT trial, is planned.
4. It would be helpful for FDA to state whether participants can choose their preferred remote location, and when such preferences could not or should not be respected (e.g., data variability and precision). Clinical trial stakeholders may be hesitant to permit participant choice of site, if there is no an affirmative statement on this issue by FDA.
5. The nature of any expected training of HCPs should be described. While specific information about the clinical trial or IP are not anticipated, is GCP-training required? Should the HCP be trained in the elements of clinical trials and clinical trial expectations (e.g., adverse event reporting, the participant’s right to refuse), and if so, need this be documented?

General comments:

1. Ambiguity exists in roles and responsibilities. As written, the investigator is responsible for the conduct of the study, but the sponsor has the responsibility for DHTs, contracted services, including “(e.g., use of mobile nurses for at-home visits, use of local HCPs, direct shipping of IP to participants).” Line 184-185. At a minimum, the investigator should be entitled to review and approve or modify relevant portions of the sponsor

contract with the vendor. Alternatively, the sponsor, not the investigator should be held accountable for the performance of its selected vendors, with appropriate attendant expectations for vendor oversight.

2. Further guidance on the role of HCPs and the boundary between a provider functioning as an HCP versus a sub-investigator (or investigator) would be helpful. The training needed for an HCP in clinical trials should be understood. If the activity is within the HCP scope of practice, does the HCP nevertheless need training and if so, what training?
3. That documentation of credentialing and practices will be necessary and sufficient for the Task Log, and what responsibilities does the PI have to validate the information provided?
4. Further guidance and explanation of the Task Log would be helpful. Often in a DCT, the local HCP is not known until the participant is identified and possibly enrolled. Much of the information on the Task Log could, therefore, be retrospectively collected, and the Task Log will need to be continuously updated.
5. Further clarity on activities that “contribute directly and significantly to the trial data” would be helpful.
6. The draft guidance acknowledges the “variability and precision of data” in DCTs. Further guidance on how to minimize the variability and how to account for sources of inconsistency, missingness, and/or bias, would be helpful, as would further explication of statistical implications of DCT data.
7. We recommend FDA update the guidance and FAQs on the expectations and appropriate completion of Form FDA 1572, as the roles, duties and configuration of those planning and conducting trials has changed markedly over time, as exemplified by the emergence of DCTs.
8. Given the growth of multi-regional clinical trials, we recommend FDA include explicit explanation of how its recommendations compare to those of other regulatory authorities (e.g., EU/EMA) and the draft ICH-E6(R3) guidance and that FDA include recommendations for alignment in DCT conduct. This would also be consistent with Congress’s mandate to FDA in the Food and Drug Omnibus Reform Act of 2022 to facilitate international harmonization of the regulation and use of decentralized clinical trials.⁵

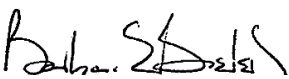
⁵ Consolidated Appropriations Act, 2023 (H.R. 2617) § 3607(c).

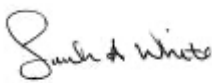
9. The glossary should define HCP, at least for the purposes listed in this draft guidance, to avoid confusion. As we interpret a technical read of the guidance, the role of the HCP is distinct from that of a sub-investigator with delegated responsibilities.


We appreciate that FDA has embodied in this guidance forward-looking, reasonable approaches to DCTs, and our comments should be taken as complementary. We believe further clarifications would strengthen the document and render it more practicable for investigators, sponsors, and third parties in furtherance of informative and efficient trials for the benefit of the health and safety of participants and the nation.


Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu, sawhite@bwh.harvard.edu, or mark.barnes@ropesgray.com) if we can be helpful or you wish to discuss.

Respectfully submitted,


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