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July 26, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2022-D-2870: Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the Draft Guidance on Decentralized Clinical Trials for Drugs, Biological Products, and Devices.¹

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical product and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

Sincerely,

/s/

Steve Berman
Sr. Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

¹ FDA, Draft Guidance for Industry - Decentralized Clinical Trials for Drugs, Biological Products, and Devices. Available at: <https://www.fda.gov/media/167696/download>.



General Comments

BIO recognizes that the COVID-19 public health emergency had an outsized impact on clinical trials, forcing many sponsors to adopt remote and decentralized trial elements to maintain trial continuity. Moreover, BIO notes that the implementation of one or more elements of decentralized clinical trials (DCTs) has the potential to improve and expedite enrollment of trials in therapeutic areas with small patient populations; improve trial population diversity to match disease population demographics more closely; mitigate logistical and financial burden for patients and caregivers; improve patient safety by reducing unnecessary exposure to infectious disease, especially for immunocompromised patients; and potentially lower trials costs for sponsors.²

As the clinical trial enterprise continues to evolve, BIO believes that the current binary the Agency uses of “traditional” versus “decentralized” is too limited and does not reflect the fact that trials may incorporate many different decentralized elements. BIO encourages FDA to consider decentralized elements as tools in a toolbox that can be deployed as appropriate depending on the therapeutic area, patient population, endpoint, and ease of product administration. Thus, BIO recommends FDA use the term “clinical trials with decentralized elements” as opposed to “decentralized clinical trials” or “fully decentralized trials.” For the sake of alignment with the draft guidance, this letter does utilize the term “DCT”.

BIO highlights that there are several potential data management and integrity issues associated with DCTs that should be further discussed in the draft guidance. These data management issues include missing or inconsistent data, identification of sources of bias, and statistical considerations such as clustering or assessing the correlation of data across sites. In addition, BIO notes that many of the challenges related to data collection and validity in clinical trials with decentralized elements are due to a lack of data standardization and interoperability between data collection modalities. BIO believes that data acquisition, transmission, quality, and reliability challenges can be reduced or eliminated when data is collected in a consistent and standardized manner and suggests FDA update the guidance to include recommendations to standardize data collection via digital health technologies (DHTs) as well as to include recommendations for sponsors and investigators to consider regarding data interoperability.

Specific Comments

1. Local Healthcare Providers (HCPs) and Trial Personnel

BIO applauds the Agency’s recommendation that local HCPs may perform trial-related assessments in DCTs. However, to implement this practice, BIO requests further guidance on the recommended or required training, oversight, and documentation FDA expects in several areas:

- Whether the sponsor or principal investigator is responsible for overseeing local HCPs;

² Ghadessi, M., Di, J., Wang, C. et al. Decentralized clinical trials and rare diseases: a Drug Information Association Innovative Design Scientific Working Group (DIA-IDSWG) perspective. *Orphanet J Rare Dis* 18, 79 (2023). <https://doi.org/10.1186/s13023-023-02693-7>



- The specific activities that local HCPs may perform, whether it varies by therapeutic area, and whether there are limits to what activities a local HCP can perform;
- How activities performed by local HCPs coincide with the protocol schedule of activities;
- How protocol deviations should be monitored;
- The expectations for training local HCPs to ensure GCP compliance; and
- Whether FDA considers local HCP activities subject to GCP inspection.

We also note that the terms used to describe trial personnel, such as “DCT personnel,” “remote trial personnel,” and “trial personnel,” are used interchangeably throughout the draft guidance. BIO requests the Agency define each of these terms so that sponsors may understand the different responsibilities and liabilities that may apply to each role or clarify if these terms are synonymous.

2. Greater Regulatory Scrutiny for Decentralized Clinical Trials

The draft guidance appears to impose numerous restrictions and requirements that are not required of sponsors in traditional clinical trials. These requirements, along with the statement that local HCPs will be less precise and more variable in conducting assessments, implies that the Agency is holding clinical trials with decentralized elements to a higher bar than traditional clinical trials. BIO requests FDA more closely align requirements for DCTs with those of traditional site-based trials.

Based upon the draft guidance’s distinction between the applicability of a DCT for a non-inferiority study compared to a superiority study,[6] the Agency appears to have more concerns regarding data quality in DCTs as compared to traditional site-based trials. While this concern may be warranted in some cases, we encourage the Agency to consider including the final guidance more balanced messaging and highlight some of the potential benefits of remote data collection such as continuous data acquisition and enhanced safety monitoring.

3. Telemedicine

BIO recognizes telemedicine as an important element in DCTs and highlights that state-level HCP licensure requirements can pose a significant barrier to the widespread adoption of DCTs. In addition, the discussion in the guidance on when a telehealth visit is acceptable should be more robust. BIO requests that the Agency identify what factors influence the types of study procedures that may be performed over video. BIO also notes that the draft guidance appears to use the terms “telehealth visits” and “remote clinical visits” interchangeably and requests the Agency clarify if these two terms are synonymous, and if not provide definitions.

4. Oversight and Compliance with Good Clinical Practice

BIO requests that the Agency provide greater detail on the roles, responsibilities, and training requirements for clinical trial personnel and ensure it aligns with Good Clinical Practice. More specifically, BIO suggests greater clarity be provided on the expectations regarding the monitoring of certain locations where in-person monitoring is not possible, such as local facilities where patients have routine labs and standard of care procedures performed.



5. Global Harmonization

Considering that clinical trials are global enterprises, BIO emphasizes the importance of including a discussion and reference on global harmonization and convergence on DCTs. BIO suggests FDA reference ICH E6(R3) Good Clinical Practice Guideline³ which is currently open for public consultation. FDA should consider issuing the final guidance following adoption of E6(R3) so sponsors may consider FDA recommendations in the context of the ICH requirements.

6. Remote Sample Collection

BIO notes that the draft guidance does not include a reference or discussion of biological sample collection at an in-home setting or consider the use of a mobile phlebotomist. BIO requests the Agency include considerations on this topic in the draft final guidance in line with other topics discussed in the guidance, such as training requirements and data integrity considerations.

7. Regulatory Engagement

BIO appreciates FDA's willingness and openness to having discussions with sponsors of clinical trials with decentralized elements. However, having upfront conversations about decentralized elements may slow down medical advancement due to long lead times for scheduling meetings coupled with long lead times for opening clinical trial sites. We encourage FDA to support timely engagement with sponsors on these issues and to provide recommendations in the final guidance on the best means of interaction to ensure feedback is effective, efficient, and does not impede drug development.

³ FDA, E6(R3) Good Clinical Practice (GCP). Available at: <https://www.fda.gov/media/169090/download>.



LINE-BY-LINE RECOMMENDED EDITS

SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 23-24</p>	<p>Original text:</p> <p>“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.”</p> <p>We believe it is important to broaden this statement beyond participant homes and healthcare facilities to encourage broad participation in clinical trials.</p>	<p>BIO recommends the following revision:</p> <p>“These trial-related activities may take place at the homes of trial participants or in local health care facilities, <u>or other locations</u> that are convenient for trial participants to encourage broad participation in clinical trials.”</p>
<p>Line 93</p>	<p>“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”</p>	<p>BIO recommends that the guidance describe situations where there may be flexibility to use alternative inspection tools, such as remote records evaluations or virtual inspections, instead of in-person inspections. There may be situations where maintaining a single physical location for inspection purposes only may not be warranted.</p>
<p>Lines 95-96</p>	<p>“This location should be listed on Form FDA 1572...”</p>	<p>BIO requests the final guidance clarify what a sponsor of a fully decentralized clinical trial should list on the 1572.</p>



SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 105-110</p>	<p>“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.”</p>	<p>BIO highlights that if the evaluation or measurement is based on a central reader (e.g., central labs or a central adjudication committee), the effect size and non-inferiority margin should not be impacted. Thus, BIO recommends the guidance be edited to read:</p> <p>“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. If the evaluation or measurement is based on a central reader (e.g., central labs or central adjudication committee), the effect size and non-inferiority margin should not be impacted. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting.”</p>
<p>Lines 210-224</p>	<p>“Sponsors should describe in the trial protocol how operational aspects of the DCT will be implemented. This description should cover... Transmission of reports on activities performed at different locations”</p>	<p>BIO suggests FDA list in data flow diagram the means for transmission of data from location-to-location vs. protocol. Moreover, operational aspects should be reflected in the operations manual and operational plans with third parties rather than the protocol.</p>
<p>Line 243</p>	<p>“Investigators are responsible for the conduct of the DCT and the oversight of individuals delegated to perform trial-related activities...”</p>	<p>BIO recommends the Agency be more specific about the oversight role by including the following:</p> <p>“Investigators are responsible for the conduct of the DCT, and the oversight of individuals (including remote trial personnel and local HCPs) delegated to perform trial-related activities...”</p>



SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 271 / 274</p>	<p>“When trial personnel contribute directly and significantly to the trial data...”</p> <p>“Local HCPs contracted to provide trial-related services...”</p>	<p>BIO recommends the roles of trial personnel be specified with the following edits:</p> <p>“When trial personnel, <u>including personnel engaged by the sponsor or investigator</u>, contribute directly and significantly to the trial data...”</p> <p>“Local HCPs contracted <u>by the sponsor or investigator</u> to provide trial-related services...”</p>
<p>Lines 300-301</p>	<p>“As part of preparing and maintaining adequate case histories, investigators must maintain a task log of local HCPs who perform trial-related activities.” See 21 CFR 312.62 and 812.140.</p>	<p>The CFR referenced requires sponsors to collect the name and address of each investigator and this requirement is being added to local HCPs without referring to them as investigators. While this distinction is understood in order to clarify the requirement not to add these local HCPs to the Form 1572, it may create ambiguity with respect to when a local HCP truly rises to the level of an investigator or not, as to whether the procedures are “trial-related activities” or routine care and if the contribution of the procedure has direct and significant impact to data or not.</p> <p>The CFR annotated references the requirement to maintain adequate medical records, which would include those written by a local HCP. Instead of requiring local HCPs be added to the task log, we propose highlighting that procedures carried out by local HCPs have appropriate case histories available in the source documentation per the CFR.</p>



SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 321-326</p>	<p>“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.”</p>	<p>BIO recommends the following edits:</p> <p>“If appropriate, specimens from trial participants (e.g., blood, sputum) may be collected by remote trial personnel, local HCPs, by patients themselves, or clinical laboratory facilities and sent to designated facilities for processing.”</p>
<p>Lines 329-330</p>	<p>“All clinical laboratory facilities should be listed on Form FDA 1572 or in the investigational plan for device studies under an IDE.”</p> <p>With the expansion of local lab facilities, this will create multiple versions and longer lists for the sites to maintain. We suggest that only the primary laboratory for each institution be listed on the Form 1572 with information about each local lab listed elsewhere (e.g., task log).</p>	<p>BIO recommends the line be edited to read:</p> <p>“All <u>primary</u> clinical laboratory facilities should be listed on Form FDA 1572 or in the investigational plan for device studies under an IDE. <u>For local labs whose activities do not significantly contribute to critical data elements (e.g., endpoint analysis) we recommend listing such facilities on the task log.</u>”</p>
<p>Lines 339-343</p>	<p>“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).”</p>	<p>BIO notes that investigators do not currently attempt to obtain reports from primary providers of routine health care today, and if interpreted conservatively this guidance may create a difficult standard. BIO recommends the sentence be amended to read: “If provided by trial participants, investigators should <u>document reports from local healthcare facilities.</u>”</p>
<p>Lines 419-420</p>	<p>“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).”</p>	<p>BIO recommends that the content of the protocol remain at a high-level when discussing preparation, handling, storage, and accountability of IP, with further details provided in a supplemental document like a pharmacy manual or other instructional manual as needed. A cross-reference statement should be included in the protocol to point to where more details can be found on this topic.</p>



SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 434-439</p>	<p>“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.”</p>	<p>This information is not usually included in the protocol, but rather in supplemental documentation such as a training plan or the Manual of Operations/Pharmacy Manual. BIO recommends that the guidance be revised to be consistent with GCPs.</p>
<p>Lines 441-442</p>	<p>“Sponsors and investigators must comply with applicable Federal, State, and international laws and regulations that address shipping IPs in their respective jurisdictions.”</p>	<p>This is the most conservative approach and leaves sponsors with having to review each state’s laws and regulations for IP and medical supply/shipping. In addition, each states’ Board of Pharmacy requires different licensing. BIO suggests FDA develop specific allowances for interstate shipment of medicinal products and devices (for both investigational and marketed products) that are under the scope of an effective IND for participants under the supervision of an investigator.</p>



SECTION	ISSUE	PROPOSED CHANGE
<p>Lines 486-504</p>	<p>“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:</p> <ul style="list-style-type: none"> • 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 • Syncing information recorded by DHTs • Serving as communication tools between DCT personnel and trial participants” 	<p>BIO notes that software used by local HCPs may not be within the control or purview of sponsors or investigators.</p> <p>BIO suggests adding to this list software used for electronic Investigator Site File and/or Source Document Repository to centralize the source generated by third parties serving as remote trial personnel for PI oversight and enabling remote monitoring.</p>
<p>Lines 509-520</p>		<p>We request the Agency provide clarification in the form of a comparison table of Task Log vs. Form 1572 on the following:</p> <p>If a local HCP is submitting for trial-related data or accessing/completing eCRFs for the study (such as partaking in assessing if a patient is eligible for screening into the study) these types of HCPs should be on the Form FDA 1572 or a task log.</p>



SECTION	ISSUE	PROPOSED CHANGE
Lines 526-531	<p>“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. If this documentation is captured in electronic form, such documentation is subject to 21 CFR part 11.”</p>	<p>BIO recommends this section be amended as follows:</p> <p>“FDA considers real-time video interactions, including telehealth, as a live exchange of information between trial personnel and trial participants. <u>Privacy and security of these real-time visits should be ensured, and the visits must be documented.</u> These live interactions are not <u>only</u> considered electronic records and, therefore, are not, <u>subject to 21 CFR part 11 if they are recorded and stored,</u> but local laws governing telehealth may apply. Privacy and security of these real-time visits should be ensured, and the visits must be documented. If this documentation is captured in electronic form, such documentation is subject to 21 CFR part 11. □”</p>
Lines 556- 557	<p>investigational product (IP): Human drugs, biological products, or devices that are being investigated in a clinical trial</p>	<p>BIO suggests the definition of IP be changed to the ICH GCP definition of IP.</p>