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August 1, 2023

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

Re: Docket No. FDA-2022-D-2870: Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability

To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments to the Food and Drug Administration (FDA or the Agency) in response to the draft guidance, *Decentralized Clinical Trials for Drugs, Biological Products, and Devices*.[1] PhRMA appreciates FDA's efforts to fulfill applicable requirements under the Consolidated Appropriations Act, 2023, to provide recommendations to advance the use of decentralized clinical trials (DCTs) to support development of drugs and devices.[2]

PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. Over the last decade, PhRMA member companies have more than doubled their annual investment in the search for new treatments and cures, including nearly $101 billion in 2022 alone.

I. General Comments

PhRMA commends the Agency for publishing this timely draft guidance. In general, PhRMA supports the recommendations put forth in this draft guidance and appreciates FDA's work to provide guidance about an important area for the future of clinical trials. We support FDA's efforts to provide additional details regarding its expectations for the design and conduct of DCTs and agree that DCTs have the potential to reduce the burden on patients, caregivers, and medical providers involved in clinical trials. We further agree with FDA that DCTs have the potential to expand access to more diverse patient populations by making use of decentralized elements[3] (e.g., telehealth, digital health technologies (DHTs), remote monitoring) that can

[1] FDA, Decentralized Clinical Trials for Drugs, Biological Products, and Devices ("Draft Guidance"). Available at https://www.fda.gov/media/167696/download.
[2] H.R.2617 Consolidated Appropriations Act, 2023, Sec. 3606a. Available at https://www.congress.gov/bill/117th-congress/house-bill/2617/text.
[3] PhRMA recommends using the term "decentralized elements" instead of the term "decentralized features" when describing elements of a clinical trial that are decentralized. The current draft guidance uses both, but PhRMA believes the term "decentralized elements" is more specific and descriptive of what the Agency is describing.

help reduce barriers to participation and reach patients who may not otherwise be able to easily access a clinical trial (e.g., due to travel, time or financial challenges, geographic location).[4]

Recognizing the role DCTs can play in reaching a broader patient population or otherwise making clinical trials more accessible, PhRMA notes that patient input should be a key factor for sponsors employing decentralized elements. To this end, we encourage the Agency to allow for flexibility in DCT protocol design and implementation to best incorporate patient input and recommend this be reflected in the guidance.

Additionally, we encourage the Agency to adopt a risk-based, flexible approach to enable DCTs and their accompanying benefits. Furthermore, we strongly agree with FDA that "regulatory requirements for investigations of medical products are the same for DCTs and traditional site-based clinical trials."[5] However, we note there are instances where the draft guidance seemingly outlines heightened regulatory expectations for DCTs as compared to traditional clinical trials. As detailed in our "Specific Comments," PhRMA suggests that FDA revise the guidance to avoid suggesting expectations or regulatory burden beyond that needed to ensure the validity of DCTs.

We recognize that there are factors unique to DCTs where additional guidance may be helpful. PhRMA believes that guidance on common impacts to trial data (e.g., sources of bias, causes of dropouts from DCTs, missing or inconsistent data on trial outcomes) as observed by FDA and unique to DCTs when compared to traditional clinical trials would be beneficial. This additional content could also include suggested approaches to address these concerns (e.g., statistical methods, including methods that account for clustering or correlation of data across sites). Such information could help sponsors in choosing appropriate strategies to address issues unique to DCTs.

In addition, given the global nature of drug development, global harmonization of regulatory expectations around DCTs is critical to advance the adoption of DCTs. PhRMA notes that the Agency has recently published draft guidance on the International Council for Harmonisation (ICH) E6(R3) Good Clinical Practice (GCP) for notice and comment.[6] We further note that ICH is currently developing a proposed Annex 2 to ICH E6(R3) that will include additional considerations on how GCP principles may be applied across a variety of trial designs and data

[4] PhRMA notes that DCTs are only one element that can help increase clinical trial diversity and should be used in conjunction with other approaches to enhance diversity and address the needs of underserved populations. To this end, there is a need to work with patients, health care providers, and clinical trial investigators to understand barriers and identify approaches to address these barriers and enhance access to clinical trials. *See* PhRMA comments in response to Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials.
[5] *See* Draft Guidance at lines 29 – 30.
[6] FDA, ICH E6(R3) Good Clinical Practice (GCP). Available at https://www.fda.gov/media/169090/download.

sources including decentralized elements.[7] PhRMA recommends that FDA work within ICH to ensure consistency between ICH guidelines and FDA's guidance.

In addition to the general comments above, PhRMA provides the following specific comments.

II. Specific Comments

A. DCT Design

As noted above, PhRMA encourages FDA to provide additional flexibility to enable the full spectrum of DCTs. For example, while the draft guidance recommends a physical location for all trial-related records for participants under the investigator's care and where trial personnel can be interviewed,[8] PhRMA believes that a physical location for trial-related records and interviews would prevent implementation of a fully site-less trial. Therefore, PhRMA recommends that a centralized location can be either physical *or* electronic. Additionally, we suggest that remote/virtual methods would be an appropriate medium to interview trial personnel as well.

DCTs offer new opportunities with respect to remote data collection, analysis, and usage, potentially leading to new ways of studying a disease. Statements in the draft guidance related to variability and precision of data obtained in a DCT appear to presuppose that, in FDA's view, data obtained remotely have more variability and may be less precise due to decentralization.[9] While we agree that data obtained remotely may be *different* from those obtained in a clinic, PhRMA does not believe this necessarily means such data will be more variable or less precise compared to data obtained via traditional mechanisms. As such, PhRMA recommends that FDA remove statements in the draft guidance suggesting that data collected in a DCT may be more variable or less precise and instead provide recommendations on standardization of processes for reduction of any increased risk of variability, in addition to the current recommendations for trial monitoring in the draft guidance.[10] Similarly, PhRMA disagrees with FDA's statement that "assessments performed by local [healthcare providers] HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel."[11] PhRMA is not aware of evidence to support this assertion and recommends that this statement be removed from the guidance as it could discourage drug developers from conducting DCTs or local HCPs from participating in DCTs.

Further, PhRMA encourages FDA to consider broadening its language about the locations of where trial-related activities may take place. For example, initial assessments and follow-ups can be conducted in locations other than the homes of trial participants or local health care

[7] ICH, E6(R3) Good Clinical Practice (GCP) Annex 2 Concept Paper. Available at https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Annex2_ConceptPaper_2023_0405.pdf.
[8] *See* Draft Guidance at lines 93 – 95.
[9] *See* Draft Guidance at lines 98 – 101.
[10] *See* Draft Guidance at lines 230 – 239.
[11] *See* Draft Guidance at lines 103 – 105.

facilities (e.g., mobile research units, community centers, pharmacies). In addition, rather than defining specific types of trial designs for which DCT approaches may or may not be appropriate, PhRMA recommends that a risk-based approach should be taken to determine which decentralized elements are appropriate to use or not. This approach would harmonize well with the approaches recommended in the ICH E6(R3) draft guideline and the EU Recommendation Paper on Decentralized Clinical Trials.[12]

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

Telehealth can be an important decentralized element of DCTs. Telehealth can provide flexibility for patients to choose a remote visit, when feasible, or allow for ad-hoc interactions. If the protocol and safety monitoring plan outline each visit type in detail, this can limit flexibility for clinical trial participants and limit the ability of investigators to enable changes to the visit method without deviating from the protocol. Accordingly, PhRMA recommends that FDA clarify in the guidance that the protocol and/or other study documents should specify the degree of flexibility for visits to be done by telehealth or in-person visits. Further, it is unclear whether a case report form (CRF) should be completed for telehealth visits when there is no data captured at those interactions (in accordance with the protocol). PhRMA suggests that while a telehealth visit should be appropriately documented (e.g., into an electronic health record), CRF documentation may not be needed in all visits, including when no data are captured.

The draft guidance distinguishes HCPs based on whether they are performing standard clinical services or protocol-specific activities. In many cases these are not separate activities. Even if an HCP is conducting standard clinical activities, such as phlebotomy, there is always an element of protocol training or lab manual training that would be needed to ensure it is done consistently and per protocol. PhRMA requests additional clarity regarding what FDA considers "detailed knowledge of the protocol or the IP [investigational product]"[13] as opposed to general knowledge. For example, PhRMA suggests that where the procedures conducted by a local HCP are consistent with commonly accepted medical practice, those activities would not be considered detailed knowledge of the protocol or IP.

Additionally, there are instances in the draft guidance where DCTs appear to be held to a higher standard than traditional clinical trials. For example, FDA recommends that investigators confirm the trial participant's identity "[d]uring each remote trial visit."[14] We are not aware of a similar recommendation to confirm patient identity at every visit for traditional clinical trials. DCTs should not be held to a higher standard than traditional clinical trials. PhRMA recommends that a participant's identity should only need to be confirmed during the first trial visit. Moreover, we suggest that the guidance be revised to clarify that a clinical trial

[12] FDA, E6(R3) Good Clinical Practice (GCP). Available at https://www.fda.gov/media/169090/download; EMA/EC, Recommendation Paper on Decentralised Elements in Clinical Trials. Available at https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf.
[13] *See* Draft Guidance at line 132 – 137.
[14] *See* Draft Guidance at line 140.

participant's identity could be confirmed by other appropriate trial personnel in addition to investigators, such as local HCPs or mobile nurses. Additionally, the draft guidance recommends that sponsors describe in the trial protocol how operational aspects of the DCT would be implemented.[15] PhRMA notes that many operational aspects would be too detailed to include in the protocol. Therefore, PhRMA recommends there be an appropriate balance of what should be in the protocol and what can be described in other operational manuals or documents and suggest this be updated in the guidance.

C. Digital Health Technologies

DHTs can play a critical role in DCTs, and PhRMA refers the Agency to our previous comments on DHTs in clinical investigations.[16] We also appreciate FDA's acknowledgement that sponsor-provisioned DHTs can be used to ensure participants are not excluded from trials solely because they do not have a protocol-specified DHT. PhRMA believes DHTs may help improve diverse participation in clinical trials when coupled with other efforts and resourced properly.[17] We also note there may be instances where DHTs are not used by all participants in a trial (e.g., single-arm trial or exploratory use) and suggest the guidance reflect this point.

D. Roles and Responsibilities

PhRMA appreciates the discussion in the draft guidance on the differentiation between trial personnel who should be listed as subinvestigators on Form FDA 1572 and trial personnel who do not need to be listed. Tying this decision to a threshold of contributing "directly and significantly to the trial data"[18] for local HCPs who should be included and excluding those who "provide trial-related services that are part of routine *clinical practice*" and do not require a "detailed knowledge of the protocol, IP, and the investigator's brochure [IB]"[19] balances the need to ensure oversight while providing sufficient flexibility to allow decentralized models to be effective. As noted above, we encourage clarity from the Agency regarding what it considers "detailed knowledge of the protocol or the IP" to better delineate which personnel should be listed on Form FDA 1572.

In addition, PhRMA recommends that the threshold for when to include laboratory facilities on Form FDA 1572 should be if the facility directly contributes to the clinical study and, in the case of local clinical laboratories, the facility is conducting more than routine clinical tests that are well-standardized. Furthermore, only the primary laboratory, provided the laboratory can trace samples to satellite or contract labs, should be listed. We also recommend that the guidance

[15] *See* Draft Guidance at line 210 and Section G.
[16] *See* PhRMA comments in response to Digital Health Technologies for Remote Data Acquisition in Clinical Investigations draft guidance. Available at https://www.regulations.gov/comment/FDA-2021-D-1128-0061.
[17] *See* PhRMA comments in response to Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials.
[18] *See* Draft Guidance at lines 271 – 272.
[19] *See* Draft Guidance at lines 274 – 279 (emphasis added).

state that in addition to collecting specimens, local clinical laboratory facilities may be used for processing of specimens for transportation and testing at a centralized location.

PhRMA encourages FDA to provide guidance on general expectations for training of individuals listed in the task log (i.e., those who provide trial-related services that are part of routine clinical practice and do not need to have detailed knowledge of the protocol, IP, or IB). Specifically, we recommend that FDA state in the guidance that the level of training of these individuals be commensurate with the contribution they make to the trial data. For example, trial personnel who contribute directly and significantly to the trial data (i.e., those who will be included on Form FDA 1572 as subinvestigators) should receive training such that they have detailed knowledge of the protocol, IP, and IB. Local HCPs listed in the task log should not require this training and it should be assumed that these individuals have a basic understanding of identifying adverse events, patient compliance issues, and product complaints. Training should emphasize the importance of timely communication of these issues to the responsible investigator, along with a mechanism to do so.

With respect to task logs, PhRMA notes that much of the documentation outlined for inclusion in the task log in the draft guidance could be captured on the Delegation of Authority (DoA) log.[20] Therefore, PhRMA recommends that the Agency clarify what information is best suited for the task log versus the DoA log. Similarly, PhRMA notes that the information in the draft guidance that is recommended to be included in the data management plan (DMP) may be captured in other related documents. PhRMA recommends that the final guidance provide flexibility on this point and recommend that the DMP or other trial-related documents (e.g., trial master file) may be a suitable place to document how sponsors expect to acquire/generate data.

We also note FDA's recommendation that CRFs "identify when and where data were collected and by whom."[21] PhRMA notes that, for traditional clinical trials, CRFs do not typically include these data; instead, these data are captured in the source documents. Further, the location of where the data are collected may not be captured in the CRFs. Accordingly, we recommend FDA revise the guidance to note that "source documents" capture information on when data were collected and by whom. We also recommend that, rather than the precise location, the source data and/or CRFs identify more generally where the data were captured (e.g., "At site" or "Remote") when including the precise location would reveal private information about the subject.

E. Investigational Products

PhRMA requests that the final guidance provide flexibility regarding the individuals who can administer an IP such as caregivers or patients if the IP's safety profile is well-characterized and

[20] Sponsors typically maintain DoA logs consistent with recommendations outlined in ICH guidelines. *See, e.g.,* ICH E6 (1996) ("The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.").
[21] *See* Draft Guidance at line 224.

does not involve complex administration procedures or specialized monitoring during the immediate period following administration. Additionally, we recommend that the language about where an IP can be administered be broadened to include locations such as mobile research units, community centers, or pharmacies. We note that the determination of where the IP is administered should not be informed by the frequency of administration, but by the benefit and risk to the patient.

In addition, PhRMA notes that the draft guidance includes a number of recommendations about information to include in the protocol regarding packaging and shipping IPs. However, consistent with standard practice, we recommend that the content of the protocol remain at a high-level with further details on IP provided in a supplemental document (e.g., pharmacy manual, manual of operations), as needed.

III. Conclusion

PhRMA appreciates the opportunity to comment on this draft guidance. PhRMA looks forward to future engagement with FDA as the Agency continues to advance the use of DCTs.

Respectfully submitted,

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