We appreciate the opportunity to comment on the FDA's Draft Guidance, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices." We are academically based investigators who have conducted multiple decentralized clinical trials (DCTs) using digital health platforms, which are identified by the below NCT numbers and accompanying PMIDs of original research manuscripts for completed DCTs and PMIDs for protocols of in-progress DCTs:

- NCT03436082; PMID for original research manuscripts: 32352038 and 35265911
- NCT04509115; PMID for protocol: 35790333
- NCT04468321; PMID for protocol: 35234659
- NCT04909229; PMID for protocol: 35940841
- NCT05214144; PMID for protocol: 36945495

In our comments, we reflect both on our own research experience as well as broader considerations in our comments below, with the hope of informing FDA as it finalizes this Draft Guidance.

II. BACKGROUND

- While we agree that DCTs may expand access to more diverse patient populations and improve trial efficiencies, FDA and those conducting DCTs must also consider how DCTs could inadvertently reduce the enrollment of diverse populations when relying on digital health technologies (DHTs). The "digital divide" related to access, familiarity, and comfort with DHTs – as well as a desire to use them – could hinder or preclude enrollment of diverse populations. We recommend that these considerations be included in Diversity Action Plans that address not only race and ethnicity (as in the April 2022 Draft Guidance), but other groups of patients, including older adults and children, people living in rural areas, people whose primary language is not English, and lower income people.
- While the FDA guidance notes that DCTs may enhance convenience and reduce the burden on caregivers, it is important to note that there may also be enrollment and participation challenges for DCTs using DHTs – such as need to rely on family members if the target study participant is not familiar or comfortable with DHTs. Therefore, while DCTs could reduce trial burden, there may also be situations where DCTs increase digital health burden. DCTs using DHTs may need to plan for additional study staff to support participants who are less comfortable with DHTs or who experience trouble with the DHT over the course of the study.
- The FDA guidance notes that DCTs may increase "retention." However, retention is not guaranteed in all DCTs, especially those that rely on real-world data (RWD) sources to ascertain trial endpoint information. For example, digital health sources that are used by DHTs, such as electronic health record (EHR) portals or portals linking data from personal digital devices, may be disconnected during the course of the DCT and require complex new methods and significant additional effort for re-authentication and reconnection. Such disconnections may occur for multiple reasons, including password changes, upgrades to these portals and security-related enhancements; these disconnections may result in a significant loss of data, which may be temporary (i.e., a gap in data that can be

addressed by having the participant reconnect) or permanent (i.e., data are lost and cannot be retrieved or the participant never reconnects). DCTs should include pre-specified plans to prepare for and address data retention. The FDA guidance notes that "up-front risk assessment and management will be key to implementing a DCT successfully" and these RWD-related challenges should be an essential part of such considerations.

III. RECOMMENDATIONS FOR IMPLEMENTING DCTS

- The FDA guidance notes that remote assessments may differ from on-site assessments when trial participants perform their own physiologic tests. We recommend that the FDA's guidance provide additional detail as to how these may differ in DCTs compared to traditional site-based trials, so that plans can be made to ensure fidelity of the acquired data. For example, remote assessments may differ in that they may not be completed at the same time or in the same setting for all study participants. Additionally, different sets of reminders may be necessary to ensure that study participants complete assessments in DCTs in a timely manner, compared to traditional site-based trials in which, for example, patients may be met by a study coordinator.
- The FDA guidance thoughtfully notes that "sponsors should ensure that DHTs used in a DCT are available and suitable for use by all trial participants." We fully agree that this is crucial to ensuring equity in trial enrollment. Additionally, the FDA guidance notes that trials may allow participants to use their own personally-owned DHTs and that trials should make devices available for patients who do not have their own. In our experience, participants who regularly use a DHT (e.g., a fitness tracker) may be reluctant to enroll in a study that requires them to switch to a different DHT that performs the same function. Where feasible, allowing participants to continue to use their own device may improve study participation.
- The FDA guidance should also address how patients who use their own DHTs may differ from patients who are provided a DHT. For DHTs that are already available on the market, patients who regularly use these tools before study participation may differ in socioeconomic status, baseline fitness level, or health behaviors than those who do not have DHTs. Additionally, we have found that many clinicians are recommending that their patients purchase DHTs to inform their care management, and so these patients may differ from the study population in other ways. These considerations should be addressed in study planning. At a minimum, study staff should record the device used and the participant's prior device experience as well as reasons for use and include these variables in study analysis.
- Further, given the often rapid evolution of DHTs, the FDA guidance should consider that subsequent versions or models of DHTs will be newly released during a study period. For example, the allocated version of a DHT may no longer be available for the DCT if the DHT is updated to a newer version, which may have additional features not available on the original DHT. DCTs using DHTs should consider and plan for the consistent availability and use of the same DHTs over time and, if newer versions are introduced, consider how these updates affect trial performance. Relatedly, DHTs that require software on the participants' phones or computers may have multiple app updates over the course of

the study. Teams must plan to follow-up with participants whenever major software updates occur, which could be multiple times over the course of the study period.

- The FDA guidance notes that patients may seek medical attention at local health care facilities and that investigators should attempt to obtain these reports from local health care facilities and from routine health care. We recommend that study teams prioritize the creation of robust plans to capture healthcare service use outside the study. If not, then significant, and very relevant, information about clinical management, and more importantly, study outcomes, are likely to be missed.
- The FDA guidance notes that sponsors should consider syncing information recorded by DHTs. As we comment above, software used in conducting DHTs may result in broken connections that need to be re-established and re-authenticated. Planning for this possibility is essential to ensure comprehensive data capture. Study teams should regularly review the completeness and quality of the DHT data over the course of the study so that remediation plans can be put in place if needed.
- The FDA guidance notes that training should be provided to all parties, including trial personnel, local HCPs, and trial participants using software to support the conduct of DCTs. Additionally, we recommend that, as appropriate, training may need to include family members or caregivers who may assist study participants in DCTs.

Again, we applaud the FDA's Draft Guidance, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" as we expect that Decentralized Clinical Trials will be critical for the clinical research enterprise going forward and appreciate having the opportunity to offer comments that may inform and improve these efforts.

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