August 1, 2023

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

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

Filed electronically at http://www.regulations.gov

Dear Commissioner Califf,

Thank you for the opportunity to provide comments to the Food and Drug Administration (FDA) on the following draft guidance issued in May 2023:

- *Decentralized Clinical Trials for Drugs, Biological Products, and Devices*

Arnold Ventures is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. Our work within the health care sector is driven by the recognition that the system costs too much and fails to adequately care for the people it serves. Our work spans a range of issues including commercial-sector prices, provider payment incentives, prescription drug prices, clinical trials, Medicare sustainability, and complex care.

We appreciate the FDA's commitment to facilitating a decentralized clinical trial (DCT) infrastructure that can enhance convenience for trial participants, reduce the burden on caregivers, and increase clinical trial enrollment among populations with limited access to traditional trial sites. We believe that DCT can help improve the engagement, recruitment, enrollment, and retention of a study population that better reflects the patient population that may ultimately use the product. To ensure strong approval standards by the FDA, we recommend that DCTs are (1) designed in accordance with prespecified trial conditions, (2) conducted such that they can be replicated in clinical care settings, and (3) monitored closely as safety signals emerge among coordinated trial sites, such as participants' homes.

Specifically, we request that the FDA provide further clarification on the following policy areas in final guidance to advance stronger pre- and post-market evidence collection through a DCT:

1. Define which medical products are most likely to benefit from centralized, hybrid, and decentralized infrastructure, and name specific patient health outcomes where the DCT approach provides more accurate or less error-prone outcome assessment;
2. Delineate design challenges that are unique to DCTs, including any predicted protocol deviations as well as needs for enhancements to coordinate clinical trial-related activities and trial-related health care professionals (HCPs);
3. Design DCTs such that trial conduct is consistent across trial sites, standardize data collection on electronic Case Report Forms, and prepare for potential protocol deviations through formal management of process changes; and
4. Clarify that clinical trial oversight includes trial-related real-time video interactions, which should be captured in electronic records for data and safety monitoring.

The draft guidance outlines specific considerations when (1) designing, (2) conducting, and (3) monitoring DCTs intended to support market authorization of drugs, biological products, and devices. The following sections detail our recommendations within the context of each of these considerations outlined by the FDA.

1. Design Considerations

The FDA should create a separate, standalone guidance for drugs and biological products that are distinct from recommendations to medical device manufacturers. Drug and device regulations are not comparable, as (1) devices have different risk-based classifications from drug classes and (2) stakeholders should expect meaningful guidance specific to the regulations related to the medical product under study. The Agency should specify for what drugs, biological products, or devices a completely decentralized trial, versus hybrid clinical trial that has some data collection in both a centralized setting and in the community, is appropriate.

Clinical trial designs determine data availability and impact the evidence standards used to determine drug safety and efficacy. The FDA should do more in final guidance to emphasize that, at a minimum, existing evidence standards for collection of clinical trial data also apply in a DCT infrastructure. The FDA should also share examples from recent experience to better describe what potential trial design challenges clinical trial participants would expect in a DCT infrastructure. This would allow diverse stakeholders to inform the FDA regulation of DCT designs and outline potential solutions to these challenges to ensure stronger evidence generation.

Design considerations outlined by the FDA in final guidance should also describe to what extent electronic capture of clinical trial data with digital health technologies is expected. This is important as the health care delivery system gains more experience with standardizing clinical practice of telehealth visits. For examples, the FDA could better delineate what clinical outcome assessments are validated in the context of a telehealth visit, describe best practices for high-quality complete data capture, and engage with patients who can inform on what further documentation created electronically from telehealth visits would be most meaningful for the FDA's review.

2. Conduct Considerations

To reach comparability between trials, which Arnold Ventures believes is of great importance to patients and to medical professionals, we recommend the FDA describe in final guidance how trial sponsors using DCTs make trial protocols more consistent with standard of care practices in the health care delivery system. Clinical trial conduct determines whether data collected are of high quality and comparable across trials. New evidence generation methods that allow fewer in-person visits to clinical trial sites (e.g., use of digital health technologies, telehealth visits) could better reflect frequency of in-person visits in clinical practice. This could lead to direct comparisons between clinical trial outcomes and outcomes seen in clinical practice.

We appreciate that the FDA acknowledges in draft guidance that data obtained in a DCT may differ from the data in a traditional site-based clinical trial, which could affect the comparability between trials' results. We recommend the FDA take this opportunity to evaluate patient outcomes in pre-approval as well as post-approval settings irrespective of the clinical trial infrastructure. This internal review could inform clinical trial protocols that have previously only

been applied in a traditional site-based clinical trial. Additionally, comparing pre-approval and post-approval outcomes may reveal that it may not be reasonable to assume comparability across clinical trial and clinical care settings.

3. Oversight Considerations

Arnold Ventures recommends that the FDA use its oversight authority to further robust data collection that fully captures health and safety concerns to inform whether new drugs and biological products are approved. Health and safety concerns could be found in Clinical Study Reports, Case Report Forms, and identified during an in-person or remote visit. We recommend that the FDA expand on requirements that trial-related information collected remotely be captured for review by a Data Monitoring Committee in final guidance after consultation with a diverse group of stakeholders including researchers, medical professionals, and patients.

Arnold Ventures recommends that the FDA do more in final guidance to explain the requirements for monitoring adverse events throughout the DCT infrastructure. Safety in human subject research must be paramount for the FDA oversight and trial sponsor's monitoring of clinical trial conduct. At a minimum, FDA must require a trial monitoring plan to (1) describe how monitoring will be implemented to assess protocol compliance, data quality, and integrity in data collection, (2) specify how the frequency with which trial records and source documents will be reviewed conforms to clinical expectations of predicted adverse events, and (3) delineate that any unique aspects related to the DCT procedures will be documented in a way that will allow the FDA to independently assess potential effects of remote trial conduct. We encourage the FDA to continue driving adoption of centralized monitoring of clinical trials to identify and proactively follow up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in clinical trial conduct.

Conclusion

Thank you again for the opportunity to comment and for your important work ensuring the safety and efficacy of human drugs and biological products. Arnold Ventures is prepared to assist with any additional information needed to address these comments in final guidance to industry. Comments were prepared by Katherine Szarama, Ph.D. Director of Health Care, and Erin Jones Health Care Manager- Drug Pricing at Arnold Ventures, with assistance from John Powers, MD.

Please contact Mark E. Miller, Ph.D. Executive Vice President of Health Care at Arnold Ventures at mmiller@arnoldventures.org or Andrea Noda, MPP, Vice President of Health Care at anoda@arnoldventures.org with any questions.

Sincerely,

Andrea Noda