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

Submitted electronically at www.regulations.gov

Re: Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability, FDA-2022-D-2870

The Association of American Medical Colleges (AAMC) is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members are all 157 U.S. medical schools accredited by the Liaison Committee on Medical Education; 13 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and the millions of individuals across academic medicine, including more than 193,000 full-time faculty members, 96,000 medical students, 153,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened the AAMC's U.S. membership and expanded its reach to international academic health centers.

I. General Comments

The COVID-19 pandemic rapidly accelerated the use of decentralized trials, increasing the need for remote medical care and clinical trial activities conducted in research participants' homes instead of a traditional clinical setting.[1] This shift also catalyzed the use of digital health technologies which has helped improve the collection, dissemination, and storage of trial data."[2] The AAMC appreciates the Food and Drug Administration's (FDA) interest in the use of decentralized clinical trials (DCTs) and hybrid trials and as discussed in our comments, we support continued efforts to better understand how DCTs can enhance the efficiency of research and recommend the FDA clarify specific aspects of the draft guidance to better ensure this goal is met.

First, we note that the draft guidance applies to "sponsors, investigators, and other stakeholders […]" and the FDA has appropriately recommended entities have early discussions with its review divisions pertaining to potential issues (e.g., feasibility, design, implementation). We propose the FDA include language in the Background of the draft guidance stating that those discussions should take place *during the design stage* of the DCT to help sponsors preemptively identify challenges and risks *well before* those issues arise (i.e., before implementation).

[1] Banks MA. Core Concept: In the wake of COVID-19, decentralized clinical trials move to center stage. Proc Natl Acad Sci U S A. 2021 Nov 23;118(47):e2119097118. doi: 10.1073/pnas.2119097118. PMID: 34789570; PMCID: PMC8617428.
[2] CDER Conversation: The Evolving Role of Decentralized Clinical Trials and Digital Health Technologies. https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-evolving-role-decentralized-clinical-trials-and-digital-health-technologies (accessed July 11, 2023).

II. Clinical Trial Diversity

The AAMC is pleased to see the FDA's recognition of the potential for DCTs to improve clinical trial accessibility and diversity, including the recommendation that sponsors "strive for diversity and inclusiveness in trial populations" through engagement, recruitment, and retention efforts. The AAMC and the AAMC Center for Health Justice (www.aamc.org/justice) have long supported efforts to improve diversity in clinical trial enrollment, offering feedback to the FDA on its patient engagement and drug development activities and the ethical inclusion and representation of participants in research.[3] We also note the alignment in this draft guidance with the FDA's recent draft guidance on sponsor development of a *Race and Ethnicity Diversity Plan*,[4] which supports new legal requirements aimed at increasing racial and ethnic diversity in clinical trial enrollment (*Diverse and Equitable Participation in Clinical Trials Act* also known as "DEPICT Act").[5] We incorporate comments the AAMC has provided to the agency with detailed recommendations on the development of its *Race and Ethnicity Diversity Plan* draft guidance.[6]

Given the government's broad commitment to advancing racial justice and equal opportunity across agencies,[7] the FDA's draft guidance should include a more comprehensive discussion of the steps sponsors (and other relevant entities) should take to meaningfully support trial diversity and inclusion. We recommend the FDA expand *Section D, Sponsor Roles and Responsibilities* (line 187-196), which only briefly mentions recruitment and retention issues. We also suggest the FDA present clinical trial diversity recommendations in an entirely separate section instead of embedded in the section on sponsor roles and responsibilities. It should also include key recommendations from the agency's draft guidance on Race and Ethnicity Diversity Plans as referenced above,[8] as well as a distillation of the steps sponsors should take to create an action plan and the timing for communicating those plans to the FDA.

III. Intergovernmental and Multi-Sector Collaboration

We recognize that the process for building capacity and expertise on the use of DCTs is complex and recommend the FDA participate in other governmental activities and community discussions convened to develop a common understanding of the deployment of DCTs across the research environment. For example, the FDA should consider joining the following efforts:

- **National Institutes of Health (NIH), National Center for Advancing Translational Science (NCATS)**
  The NIH is building capacity for the design and deployment of DCTs across its 27 Institutes and Centers and in March 2023 the agency issued a request for information on ways to accelerate the use of DCTs.[9] The AAMC commented on this request, recommending timely collaboration with the

[3] See AAMC comments to FDA, Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, https://www.aamc.org/media/11451/download (August 2019); AAMC comments to FDA, Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments (September 2022) https://www.aamc.org/media/63181/download?attachment.
[4] FDA Draft Guidance, Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials (April 2022).
[5] H.R.6584 - DEPICT Act, Diverse and Equitable Participation in Clinical Trials Act, https://www.congress.gov/117/bills/hr6584/BILLS-117hr6584ih.pdf.
[6] AAMC comments to FDA, Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry (June 2022), https://www.aamc.org/media/61296/download?attachment.
[7] See AAMC Comments to OMB, Request for Information: Methods and Leading Practices for Advancing Equity and Support for Underserved Communities Through Government, OMB 2021-0005, https://www.aamc.org/media/55326/download?attachment.
[8] Supra Note 3.
[9] National Institutes of Health, National Center for Advancing Translational Sciences , Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials (NOT-TR-23-006, March 2023).

FDA's efforts given the temporal proximity of both requests for comment on DCTs and the overlap in topics/issues addressed.[10]

- **White House, Office of Science Technology and Policy (OSTP)**
  The OSTP is developing a strategy to "advance innovation and enhance the responsiveness of [the U.S.] clinical trials infrastructure," including ways to better account for preparedness, equity and diversity.[11] To inform this effort, the OSTP issued an RFI identifying key barriers to the transition from DCTs to a single clinical trial protocol that would be simultaneously implemented across the research community. It is important for the FDA to consider the ongoing efforts of OSTP, NIH, and other agencies to evaluate DCTs and related initiatives.

- **FDA and Duke-Margolis Center for Health Policy**
  As the FDA is likely aware, the agency has partnered with Duke University to convene workshops on digital health technologies that support clinical trials.[12] Given the rapidly developing digital health landscape and the FDA's recommendations on digital health technology included in the draft guidance (*Section C*), we note that the draft guidance documents supporting the recommendations in this section (*Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations* (*March 2023*); *Clinical Decision Support Software* (*Sept. 2022*)*; Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (*Dec. 2021*)) are not yet finalized. We encourage the FDA to expeditiously finalize these guidance documents.

IV. Areas for Improvement in Draft Guidance

In our comments below, we outline several issues/topics in the draft guidance that would benefit from clarification and/or additional public input to minimize confusion and ensure successful implementation:

- **DCT Design** (*Section A*)
  The FDA states that "[f]or inspectional purposes, there should be a physical location for all clinical trial-related records for participants under the investigators care are accessible and where trial personnel can be interviewed. This location should be listed on Form FDA 1572 (lines 93-94)."
  The FDA should consider whether the recommendation for *only one* location has the potential to be burdensome for trial personnel (e.g., whether a single location is feasible or difficult for an investigator in a different locale to access and whether there are virtual options that might offer the same interaction in fulfillment of this inspection process).

- **Remote Clinical Trial Visits and Related Activities** (*Section B*)
  - **Participant's home/preferred location** - The FDA states that in person and trial-related activities should be conducted by personnel sent to the participants home or a preferred location. However, the guidance does not specify which member of the clinical trial team has the authority to make this determination nor does it provide recommendations on how those decisions are made, including whether research participants have the ability to select the preferred location. The benefits and burdens of home health visits should also be a part of the decision-making process and included in the trial protocol. For example, some individuals might be uncomfortable with an investigator or research staff in their home or community and might prefer an alternative mode or location for interaction. Individuals might also require additional supportive visits if the

[10] AAMC comments to NIH, Request for Information (RFI) from the National Center for Advancing Translational Science (NCATS): Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials, NOT-TR-23-006 (May 2023), https://www.aamc.org/media/67381/download?attachment.
[11] See AAMC Comments to OSTP, Emergency Clinical Trials RFI (January 2023), https://www.aamc.org/media/64816/download?attachment
[12] Meetings Examine Impact of Healthcare Algorithms on Racial and Ethnic Disparities in Health and Healthcare, https://effectivehealthcare.ahrq.gov/news/meetings (accessed July 13, 2023).

lack of connection with a health care facility is worrisome or disconcerting. Finally, consideration should be given to the safety and/or comfort level of the research staff which might include the safety of the home and/or neighborhood of the research participant.

- **Qualified trial personnel** - The FDA indicates that trial-related activities should be conducted by "qualified trial personnel who have been appropriately trained" (lines 135-138). However, the agency does not provide examples or supporting criteria that would help sponsors determine whether trial staff are "appropriately trained" (e.g., licensure and professional training requirements, impact of local laws, standard of care, privacy and safety risks, conducting telehealth visits).

- **Digital Health Technologies (DHTs)** (*Section C*)
  - **Privacy and confidentiality** - This section provides important guidance on the remote transmission of data but does not clearly address privacy and security issues, including the collection and protection of personal data (e.g., data parsimony, data quality, development of data management plans, informed consent, data sharing, and data access). The FDA should consider adding a separate section dedicated to privacy, confidentiality, and the potential risks to research participants. It should also be noted that these issues should be addressed in the informed consent form and protocol itself.[13]

  - **Equitable Access to DHTs** - The FDA recommends that sponsors "ensure that DHTs used in a DCT are available and suitable for use by all trial participants" (line 170-172) but does not elaborate on ways sponsors can achieve this goal. In previous comments to the FDA, we have raised concerns about difficulties accessing DHTs (e.g., mobile/wearable technology) for certain populations such as individuals from historically marginalized communities. It is imperative for the FDA to clearly articulate potential roadblocks for equitable access to DHTs in the draft guidance and related educational material (e.g., FAQs).

  - **Ongoing Interaction with Research Participants** – It is important that opportunities for participant interaction allow for the ongoing exchange of information between the study participant and investigator and create opportunities for the investigator to answer questions or address concerns that might arise during the course of the clinical investigation. Face-to-face participant and investigator interaction throughout the duration of a clinical trial is equally important as creating opportunities to reduce or replace study visits with technology.

  - **Additional Considerations**
    The draft guidance should address other challenges related to DCTs and DHTs, especially those raised in the agency's recent AI/ML Discussion Report and in comments received in response to this draft guidance. The FDA should also take into account the lessons learned from clinical trials conducted during the COVID-19 pandemic that deployed innovative methods for engaging and communicating with potential research participants.

- **Roles and Responsibilities of the Sponsor and Investigator** (*Section D*)
  The FDA provides an overview of sponsor and investigator responsibilities, including the oversight and delegation of clinical trial activities. However, several issues remain unaddressed or would benefit from additional clarification:
  - Third party selection and oversight, including example criteria for assessment and selection
  - Investigator responsibilities for home health visits

[13] FDA Draft Guidance, Digital Health Technologies for Remote Data Acquisitions in Clinical Investigations, FDA-2021-D-1128 (Dec. 2021).

- Appropriate training and education to perform trial related activities
- Factors for determining whether the trial will take place at a participants home or another preferred location.

- **Informed Consent and IRB Oversight** (*Section E*)
  Information conveyed to research participants – The FDA should buttress the informed consent recommendations with guidance on ethically appropriate mechanisms to obtain consent, including what information should be conveyed to participants during the consent process (e.g., use of personal data).

  - **Special populations** – The FDA should include recommendations that the informed consent form include a separate section addressing issues unique to "special populations" (e.g., children, pregnant and lactating persons, prisoners).

V. Ongoing Evaluation and Agency Accountability

In closing, we recommend the FDA prioritize a plan to routinely evaluate the effectiveness of DCTs, including the impact of this draft guidance. To ensure this guidance and other potentially related guidance and/or supplementary materials take into account the recommendations and findings from other government efforts to assess DCTs and DHTs, the FDA should take immediate steps to join these discussions, especially as the agency finalizes this guidance. Further, to assist with the development of an internal evaluation plan, we recommend review of the Government Accountability Offices' new report, *Evidence-Based Policymaking: Practices to Help Manage and Assess the Results of Federal Efforts*,[14] and the report from the Commission on Evidence-Based Policymaking, *The Promise of Evidence-Based Policymaking* (see also, AAMC comments to the Commission).[15] [16]

We appreciate the opportunity to comment on this important endeavor and believe that the FDA would sincerely benefit from ongoing community expertise to help the agency address specific issues raised in commenters responses to this draft guidance and related public forums. We would be happy to offer additional information on any of the recommendations offered in this letter. For questions, please contact me or my colleagues Daria Grayer, Director for Regulation and Policy & AAMC Center for Health Justice Director of Policy (dgrayer@aamc.org), Heather Pierce, Senior Director for Science Policy & Regulatory Counsel.

Sincerely,

Ross McKinney, MD.
Chief Scientific Officer

cc: David J. Skorton, MD, President and Chief Executive Officer

[14] Evidence-Based Policymaking: Practices to Help Manage and Assess the Results of Federal Efforts https://www.gao.gov/products/gao-23-105460 (accessed July 25, 2023).
[15] The Promise of Evidence Based Policymaking, https://bipartisanpolicy.org/download/?file=/wp-content/uploads/2019/03/Full-Report-The-Promise-of-Evidence-Based-Policymaking-Report-of-the-Comission-on-Evidence-based-Policymaking.pdf (accessed July 25, 2023)
[16] AAMC Comments to Commission on Evidence Based Policymaking, https://www.aamc.org/media/12066/download