May 12, 2023

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

Responses submitted via webform

The AAMC (Association of American Medical Colleges) 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. Application of Research Methods in Decentralized Clinical Trials

The AAMC appreciates the National Center for Advancing Translational Sciences' (NCATS) interest in receiving feedback on ways decentralized clinical trials (DCTs) can "accelerate the implementation of clinical trials," including key factors to consider when designing and deploying a DCT. We support the broader goals of this request for information (RFI) — to identify ways DCTs can increase clinical trial enrollment by enabling participation from diverse backgrounds including "but not limited to race, ethnicity, socioeconomic status, background, gender, and mental or physical ability" and individuals from marginalized racial and ethnic groups. As emphasized throughout our comments, we believe inter-governmental collaboration, robust multi-sector alignment, and the active inclusion of state and local community voices should serve as a primary foundation as NCATS takes next steps "to advance the ability to perform decentralized trials or hybrid trials."

Utilizing of Community Wisdom to Inform Research Methods

The AAMC and the AAMC Center for Health Justice (www.aamchealthjustice.org)[1] have long supported the inclusion of diverse populations in clinical trials. In previous comments to federal agencies, we have recommended agencies create additional opportunities to broaden trial participation, helping to address the systemic inequities that result from lack of representation of diverse racial and ethnic groups in clinical research. Streamlining and coordinating federal diversity efforts can also help ensure that related activities (e.g., proposed guidance, regulations, or development of programs) do not reside solely in one center/institute within an agency. This is especially important when shared decision-making is essential for developing capacity and awareness related to a particular issue or topic such as DCTs (see, AAMC comments FDA, Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, June 2019,[2]

[1] AAMC Center for Health Justice, About Us: https://www.aamchealthjustice.org/.
[2] Re: Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry; Availability, Docket No. FDA-2019-D-1264, August 6, 2019, https://www.aamc.org/media/11451/download.

see also, AAMC comments, FDA, Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments, September 2022).[3]

As further described below (Section 3. Community Engagement), we also urge NCATS to ensure that the populations closest to historic and contemporary injustice are included in the design, implementation, and evaluation of DCTs. To achieve this goal, NCATS should create a permanent pathway for bi-directional community and patient engagement, similar to FDA's Office of Patient Affairs, established to "play a key role in the internal coordination of the data submitted to the Agency in addition to serving as a central entry point for industry, patients, and other stakeholders" (see, AAMC Comment Letter, Patient Focused Drug Development: Collecting Comprehensive and Representative Input, September 2018).[4] This will help support NCATS' interest in building public trust and accountability through feedback from "patient and lay communities." It also supports the equitable and socially conscious implementation and use of DCTs across Clinical and Translational Science Awards (CTSAs) and the broader research enterprise.

Inter-Government Coordination

As articulated above, we recognize that the process for building capacity and expertise on the use of DCTs and digital health technology (DHT) is complex. We also appreciate that the development of consistent policies, procedures, and educational tools across the NIH, its 27 Institutes and Centers, and other federal agencies is not a one size fits all approach. In the AAMC and the AAMC Center for Health Justice's response to federal requests for information on similar topics, we frequently emphasize the adoption of a transparent, multi-sector approach (e.g., including sponsors, academic research institutions, professional societies, community organizations, advocacy groups) to leverage existing networks of connected entities (see AAMC Comments to OSTP Emergency Clinical Trials RFI, January 2023).[5] We include this recommendation again here, especially since it would help NCATS gain a deeper understanding of the complex interplay of the clinical research enterprise (e.g., clinical and translational processes, workflow integration and operationalization, data integration platforms, system interoperability).

Further, while NCATS is likely aware of the numerous activities taking place across both the federal government and public-private sector to design and deploy remote trial sites, we would like to highlight one example of a multi-sector collaboration intended to promote "shared learning and consistency regarding DHT-based policy, procedure, analytic tool development" — the FDA's *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development* (see Framework Report).[6] The report provides an overview of the current landscape of DHTs and outlines the steps FDA will take to fulfill its goals: including significant community engagement opportunities, development of external programs to ensure consistency of DHT evaluations, and issuance of draft guidance which notably includes FDA's recent DCT draft guidance issued in May 2023 (*Decentralized Trials for Drugs, Biological Products, and Devices*).

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[3] AAMC Comments, Re: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments; Docket No. FDA-2018-N-2455 (September 27, 2022), https://www.aamc.org/media/63181/download?attachment.

[4] See, AAMC Comment Letter, Patient Focused Drug Development: Collecting Comprehensive and Representative Input; Draft Guidance for Industry (September 11, 2018). https://www.aamc.org/download/492188/data/aamccommentletteronpatientfocuseddrugdevelopment.pdf

[5] AAMC Comments, Re: OSTP Emergency Clinical Trials RFI, January 27, 2023, https://www.aamc.org/media/64816/download?attachment.

[6] Food and Drug Administration, Framework for the Use of Digital Health Technologies in Drug and Biological Product Development, https://www.fda.gov/media/166396/download (Accessed May 12, 2023).

Given the timeliness of the NCATS' RFI and analogous issues raised in the FDA's DCT draft guidance and DHT Framework, it would benefit NCATS to coordinate with FDA if not already engaged on these issues.

Key Factors When Deploying DCTs and DHTs

The rapid proliferation of technology has had a substantial impact on clinical research. In addition to other key factors, we note the following:

- **Remote Data Monitoring —** DCTs require methods and strategies for remote data monitoring and capture, along with tools to increase data quality and safety. NCATS could develop or contribute to recommendations on how artificial intelligence (AI) might impact patient experience, including the impact of structural bias and racism in machine learning.

- **Informed Consent** — Consider methods of ensuring informed consent are both appropriate for and reflective of the clinical trial design of a DCT. Considerations should also include an evaluation of ethically appropriate mechanisms to obtain consent, including what information should be conveyed to potential participants (e.g., data use and data access). Seek to better understand the lessons learned from clinical trials initiated or conducted during the COVID-19 pandemic that deployed innovative methods for engaging and communicating with potential research participants.

- **Access to Technology —** In previous comments to FDA, the AAMC has expressed concerns related to unequal access to mobile technology by research participants and the lack of financial support to permit participant use of such technology (e.g., smart phones, smart watches, computers, tablets). We have noted that face-to-face participant/investigator interaction throughout the duration of a clinical trial is equally important as creating opportunities to reduce or replace study visits with technology (e.g., In comments to the FDA we note: "[e]nsuring opportunities for participant interaction allows for the ongoing exchange of information between the study participant and investigator and creates opportunities for the investigator to answer questions or address concerns that might arise during the course of the clinical investigation." See *AAMC Comments to FDA on the Use of Electronic Records and Signatures in Clinical Investigations*).[7] NCATS should examine other structural challenges to clinical trial participation, such as the disparate needs of rural and urban populations that have resulted in a "digital divide." There should also be a recognition of the need for continued access to IT support during a DCT if participants need technology assistance. This will help ensure timely access to clinical trial alerts (e.g., safety updates), as well as the quality of trial results.

- **Barriers to Trial Participation**— Consider how the engagement and communication with populations with low literacy or limited English proficiency would be impacted by a DCT model, particularly those taking place on electronic platforms. Other factors such as historical distrust of the healthcare system should be considered as a potential barrier to participation, especially for Black, Hispanic, and other groups that have been historically excluded from clinical trials.

- **Delegation of Responsibilities and Training—** An examination of the benefits and burdens of home health visits should be considered, including the level of participant comfort. For example, some individuals might not feel comfortable with an investigator/research staff in their private homes or surrounding communities and would prefer alternatives through use of technology, while others might require additional supportive visits if the lack of connection with a health care facility is worrisome or disconcerting.

[7] AAMC Comments: Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11—Questions and Answer; Draft Guidance for Industry; Availability (Docket No. FDA-2017-D-1105), August 21, 2017. https://www.staging.aamc.org/download/482250/data/useofelectronicrecordscommentletter.pdf.

II. Resources, Infrastructure, and Enabling Technologies

Inter-Agency Coordination & Digital Health Technology

Through this RFI, NCATS has correctly identified the immediate need to understand the most common operational challenges and technological needs for DCTs. One possible opportunity for immediate inter-agency engagement on this issue is through the FDA and Duke-Robert J. Margolis, MD Center for Health Policy workshop series on digital health technology to support clinical trials ("*Understanding Priorities for the Use of Digital Health Technologies to Support Clinical Trials for Drug Development and Review*").[8] The collaboration with FDA through a public workshop series would benefit attendees that conduct or participate in *both* FDA and NIH supported research. This series also overlaps with many of the issues the NIH's National Institute on Minority Health and Health Disparities and HHS' Agency for Healthcare Research and Quality will discuss at the upcoming meeting (May 15, 2023) on the impact of healthcare algorithms on racial and ethnic disparities in healthcare.

Clinical Trial Infrastructure

NCATS is also interested in resources and technologies that support the broader clinical trial infrastructure. Exacerbating existing infrastructure shortcomings, the COVID-19 pandemic amplified the need for a more coordinated national pandemic response, including a more cohesive approach to rapidly conducting clinical trials. It also magnified profound and disparate impacts on populations generally underrepresented in research and the need for a national, standardized data collection system that accurately captures race and ethnicity data and related information to ensure equitable pandemic preparation and response to future health threats.[9] [10] In response, the White House Office of Science Technology and Policy (OSTP) is currently developing an ambitious 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 (see, Preparing U.S. Clinical Trials Infrastructure for Emergencies: A White House Virtual Roundtable Discussion, January 2023).[11]

In response to the OSTP's request for comment on this activity, the AAMC expressed support for the direction to "rapidly carry out coordinated, large scale clinical research,"[12] emphasizing potential challenges to successful implementation and recommending a multi-sector approach to achieve consensus on key issues such as clinical trial agreement terms. We also recommend that NCATS not initiate any unique programs without consideration of the ongoing efforts and input the broad research community has already provided in response to this multi-agency coordination effort.

The AAMC has recognized NCATS' unique role in such an effort, especially through the CTSA Program, noting to OSTP that:

> "Not only can these networks and consortia extend the number of potential research sites, they can also provide OSTP with considerable information about the advantages and challenges with implementing a single protocol or process across a set of organizations with already-established connections. As one key example, the Clinical and Translational

[8] Public Workshop: Understanding Priorities for the Development of Digital Health Technologies to Support Clinical Trials for Drug Development and Review, https://www.fda.gov/drugs/public-workshop-understanding-priorities-development-digital-health-technologies-support-clinical#event-information (Accessed May 9, 2023). The second workshop will take place May 28-29, 2023 and will be discussing diversity, engagement and report trial measurements among other topics. *Id*.
[9] AAMC Press Release, AAMC Calls for Enhanced COVID-19 Data Collection on Health Disparities, April 10, 2020 https://www.aamc.org/news-insights/press-releases/aamc-calls-enhanced-covid-19-data-collection-health-disparities (Accessed March 8, 2023).
[10] Alberti PM, Lantz PM, Wilkins CH (2020) "Equitable Pandemic Preparedness and Rapid Response: Lessons from COVID-19 for Pandemic Health Equity" J Health Polit Policy Law 8641469. https://doi.org/10.1215/03616878-8641469.
[11] Preparing U.S. Clinical Trials Infrastructure for Emergencies: A White House Virtual Roundtable Discussion, January 6, 2023.
[12] Supra Note 5.

Science Awards (CTSA) Program administered by the National Center for Advancing Translational Sciences (NCATS) was developed to address precisely the kinds of challenges and inefficiencies in translational research that OSTP seeks to address with this current effort. Engaging with both NCATS and CTSA institutions would be instrumental in assessing the utility of using this network or working to create new models for connecting institutions."

As illustrated throughout these comments, we appreciate the numerous opportunities and initiatives designed to improve the clinical research enterprise — from the OSTP's infrastructure initiative discussed above, FDA's roadmap for DHTs and draft strategy for DCTs, and NCATS' efforts to improve the efficiency and diversity of clinical research through DCTs —and urge federal coordination. A lack of coordination would pose an unfortunate missed opportunity.

III. Community Engagement and Partnerships

A core component of this RFI is "identifying the needs of participants, in particular those whom traditionally experienced health disparities or in an underserved population, to participate in DCTs." The AAMC and the AAMC Center for Health Justice are champions for the development of broad bi-directional channels of communication with community partners and suggest the following to achieve this goal:

- **Mechanisms for Community Feedback** — Implement mechanisms for dynamic community feedback on the next steps for this RFI (e.g., strategy, guidance), including implementation and evaluation of those activities (e.g., development of metrics that matter both to NIH/NCATS and applicable to diverse communities).

- **Community Anchors** — In furtherance of the above, one mechanism could be the establishment of a *permanent* role for "community anchors" to proactively engage with individuals and communities that have been historically and socially marginalized. Community anchors are trusted, respected, and knowledgeable individuals, institutions, or organizations from a specific community that would help NCATS facilitate meaningful interaction between the NIH/NCATS and the individuals and/or communities it would like to partner with.

- **Building Community Trust** — Community partnerships are most successful when they are built on trust, respect, and a shared vision. The AAMC Center for Health Justice, in partnership with community members, co-developed the *Principles of Trustworthiness* and a corresponding toolkit to guide organizations, including government entities, in their efforts to equitably partner with communities and build trust among members of those communities. These principles integrate local perspectives with established precepts for community engagement. NCATS has indicated that it would like to understand the social and/or cultural nuances of communities, including "establishing knowledge and procedures to co-design studies with communities," as well as partnerships and collaborations with diverse communities. It is important for NCATS to recognize that the process of engagement is just as important as the product, and recommend utilization of a process such as the Principles of Trustworthiness to facilitate discussions with community members to co-design culturally appropriate DCT strategies and recommendations.[13]

[13] AAMC Center for Health Justice, Principles of Trustworthiness, https://www.aamchealthjustice.org/our-work/trustworthiness/trustworthiness-toolkit#toolkit.

- **Additional Avenues for Community Feedback** — NCATS could create avenues for broader community members to receive feedback outside of the normal channels of communication, especially for those that do not typically follow the Federal Register or official communications from NIH about funding opportunities and notices.

- **White House Efforts to Advance Racial Equity** — NCATS should coordinate with the Administration's current efforts to advance equity across the federal government in support of Executive Order 13985 (*Advancing Racial Equity and Support for Underserved Communities Through Federal Government*, see, White House Press, Feb. 2023).[14] Notably, one area of focus is the prevention and remedy of algorithmic discrimination against people based on actual or perceived race, ethnicity, sex, religion, age, an issue of importance to the NIH as well.

We appreciate the opportunity to comment on this important endeavor and would be happy to offer additional information on any of the recommendations discussed in our letter or answer any questions related to the ways NIH/NCATS could utilize the AAMC Center for Health Justice Principles of Trustworthiness and related toolkit. For any questions related to these comments, please feel free to contact Chief Scientific Officer Ross McKinney, MD (rmckinney@aamc.org) or Director for Regulation and Policy Daria Grayer, JD, MA (dgrayer@aamc.org).

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[14] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government, https://www.whitehouse.gov/briefing-room/presidential-actions/2023/02/16/executive-order-on-further-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/ (Accessed May 9, 2023).