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Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments; Docket No. FDA-2018-N-2455

Submitted electronically at www.regulations.gov

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 comprise all 156 accredited U.S. medical schools; 14 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and nearly 80 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 191,000 full-time faculty members, 95,000 medical students, 149,000 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. Learn more at aamc.org.

The AAMC appreciates the Food and Drug Administration (FDA)'s longstanding commitment to better understand how patients, researchers, medical product developers, and others can collect and use patient input (including "patient experience data"[1]) to inform medical product development and regulatory decision-making. The AAMC has offered support for these efforts in response to the FDA's first guidance in the Patient Focused Drug Development (PFDD) series ("*Collecting Comprehensive and Representative Input*"),[2] and other guidance on addressing barriers to the recruitment and retention of underrepresented populations in clinical trials.[3]

In this draft guidance (Guidance 3), the FDA provided expansive and detailed recommendations on approaches for the selection and modification of "clinical outcome assessments" (COAs) to "measure outcomes of importance to patients in clinical trials." In the comments below, we provide recommendations on three areas that we believe are important as the FDA takes steps to finalize this draft

[1]" 'Patient experience data' is defined for purposes of this guidance in Title III, Section 3001 of the 21st Century Cures Act, as amended by section 605 of FDARA, to include data that "(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers); and (2) are intended to provide information about patients' experiences with a disease or condition, including (A) the 'impact (including physical and psychosocial impacts) of such disease or condition or a related therapy or clinical investigation; and (B) patient preferences with respect to treatment of the disease or condition."

[2] AAMC Comments, *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input*; Draft Guidance for Industry, Docket No. FDA-2018-D-1893 (September 11, 2018), https://www.aamc.org/system/files?file=2019-07/AAMC-%20Comment-Letter-Patient-Focused-Drug-Development-Sept112018.pdf.

[3] AAMC Comments, *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry*, Docket No. FDA – 2021 – D – 0789 (June 13, 2022), https://www.aamc.org/media/61296/download?attachment; see also: AAMC Comments, *Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry*, Docket No. FDA-2019-D-1264 (August 6, 2019), https://www.aamc.org/media/11451/download.

guidance and other guidance in the PFDD series. These include intra-agency and government-wide coordination, public input and timing for sponsor interaction with the FDA, and additional considerations.

I. Intra-Agency and Government-Wide Coordination

Coordination across FDA

In previous recommendations, the AAMC has emphasized the need for increased expansion and coordination of patient engagement activities across the FDA. In our response to the 2017 request for comments on the establishment of the FDA's *Office of Patient Affairs (OPA)* in the Office of the Commissioner, we supported the important role the OPA would play in the enhancement of patient engagement activities, noting the immediate need for a "central entry point" to facilitate internal coordination and public engagement.[4] Since establishment of the Office, we are pleased to see a notable increase in patient engagement initiatives through advisory committees, public private collaborations and partnerships, community town hall meetings, public health symposiums, and opportunities for public comment on proposed guidance and regulation.

The OPA plays a critical role in intra-agency collaboration, especially in the coordination between the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research. While the FDA has substantially increased the visibility of the OPA, the specific role the Office plays in the coordination and use of patient experience data and public dissemination of guidance and regulation both internally and externally is an area that could use attention. Continuing to highlight the specific role and activities of the Office at intra-agency convenings, as well as community town hall and patient advisory meetings, would help support meaningful collaboration and increase communication with diverse stakeholder groups (e.g., minority serving health professional organizations and advocacy groups[5]).

Coordination with Government-Wide Initiatives

The AAMC supports the Federal Government's commitment to advancing an equitable government (see, Executive Order (EO) 13985, *Advancing Racial Equity and Support for Underserved Communities Through Federal Government*), and believes the FDA's current interest in increasing diverse representation and input in medical product development and regulatory decision-making directly supports the government's commitment to racial justice and equity.[6] As the FDA takes steps to finalize the PFDD guidance series and other patient engagement guidance, we suggest the FDA consider the following recommendations:

- Coordinate patient engagement and participant diversity activities with current efforts to advance equity and justice across the Federal Government. This could be accomplished through the Office of Patient Affairs and HHS' broader effort to "*[…] Advance Equity in the Delivery of Health and Human Services.*"[7] Related, the FDA has recently issued draft guidance recommending sponsor development of a *Race and Ethnicity Diversity Plan* to increase the enrollment of participants from underrepresented racial and ethnic populations.[8] To assist the regulated community, we recommend

[4] AAMC Comments, *Enhancing Patient Engagement Efforts Across FDA*, Docket No. FDA-2017-N-0455 (June 12, 2017), https://www.aamc.org/media/13126/download.

[5] In previous comments to the FDA, we urged the FDA to ensure that patient advocates and patient representatives engaged in these activities are not solely professional advocates selected, trained, or funded by drug, device, and biotechnology companies. See AAMC Comments, Supra Note 4.

[6] AAMC Comments on *Methods and Leading Practices for Advancing Equity and Support for Underserved Communities Through Government*, OMB 2021-0005 (July 2, 2021); https://www.aamc.org/media/55326/download?attachment; see also: *Biden-Harris Administration Releases Agency Equity Action Plans to Advance Equity and Racial Justice Across the Federal Government* (April 14, 2022).

[7] Press Release, *HHS Statements on New Plan to Advance Equity in the Delivery of Health and Human Services* (April 14, 2022), see also, Department of Health and Human Services, *Equity Action Plan.*

[8] AAMC Comments, *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials*, Docket No. FDA-2022-D-0789 (June 13, 2022), https://www.aamc.org/media/61296/download?attachment.

the FDA better connect these two efforts by including an explanation of the requirements of the *Race and Ethnicity Diversity Plan* (once finalized) in the PFDD guidance, particularly in the PFDD Roadmap as described in Section II (below).

- Coordinate the FDA's data collection activities with the government's current initiatives to promote evidence-based policy and regulation through equitable data collection (see, White House *Memorandum on Restoring Government Through Scientific Integrity and Evidence-Based Policy Making*[9] and the Office of Management and Budget Press Release on the revisions to the statistical standards (Directive No. 15) for collecting race and ethnicity data.[10]

- Participate on or collaborate with the *White House Equitable Data Working Group*, established under EO 13985 to "[…] outline a strategy for increasing data available for measuring equity and representing the diversity of the American people and their experiences." The activities and output from this Working Group are especially applicable to the collection and evaluation of COA data and development of an evidence-based rationale for utilization of COAs.[11]

- Identify additional resources that would assist the FDA with the continued development of an ethical framework for patient engagement, recruitment, and retention in clinical trials (e.g., April 2022 recommendations from the National Academies of Science, Engineering, and Medicine on *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*).

II. Timing of Sponsor Interaction and Defining Concept of Interest

Sponsor Interaction with FDA

Throughout the draft guidance, the FDA emphasizes the need for sponsors to "[…] seek […] input *as early as possible* […] throughout medical product development to ensure COAs are appropriate for the intended context of use (*emphasis added*)." The FDA also delineates the need for early interaction with the Agency to "[…] obtain feedback from the relevant FDA review division when considering collection of patient experience data related to the burden of disease and treatment."

We agree this communication should begin "as early as possible" in the clinical trial or medical product development process. However, we encourage the FDA to provide specific examples and supporting rationale regarding *when* sponsors should communicate with the FDA. We recommend that communication should be expected to begin prior to the development of the recommended "Roadmap to Patient-Focused Outcome Measurement in Clinical Trials" or at minimum, during Stage 1 (Understanding the Disease or Condition) when it already recommended that sponsors obtain feedback from patients, caregivers, subpopulations, experts, and others.[12]

Timing for Patient and Caregiver Engagement

In Section III of the Draft Guidance, the FDA provides detailed recommendations on the steps sponsors should follow when identifying, defining, and assessing COAs. Notably, Step 1 ("*Understanding the Disease or Condition*") and Step 2 ("*Conceptualizing Clinical Benefits and Risks*") are heavily reliant on

[9] *Memorandum on Restoring Trust in Government Through Scientific Integrity and Evidence-Based Policymaking* (January 27, 2021).
[10] *OMB Launches New Public Listening Sessions on Federal Race and Ethnicity Standards Revision* (August 30, 2022),
[11] Final Report, *Recommendations from the Equitable Data Working Group* (April 22, 2022).
[12] This recommendation is consistent with the AAMC's comments to the FDA in response to an the April 2022 Draft Guidance on improving trial diversity (Docket No. FDA–2021–D–0789); "To better ensure the FDA conducts a thorough review of whether sponsors' goals are being met, we recommend that the FDA specify that identification of enrollment goals take place *prior to the commencement of research* (i.e., during the development of the Plan), instead of 'as early as practicable in clinical development.' This would also allow for sponsors to define enrollment goals with input from community members and community-based organizations."

input from patients and/or caregivers to understand the manifestations of the disease and aspects of the patient's experience with the disease or condition.

The FDA should provide explicit guidance on how sponsors are expected to involve patients and caregivers throughout the Roadmap, from the design of the Roadmap to the selection and development of COA outcomes. This would help to facilitate a necessary redefinition of "patient engagement" — shifting the perspective of patients being viewed solely as study participants to partners and co-developers.

III. Additional Considerations

Proxy-Reported Outcome Measures

The FDA discourages sponsors from using a "proxy-reported outcome measure," which is when "[…] someone other than the patient reports on patient experiences as if the individual were the patient." This rationale is based on the fact that "it is impossible to collect valid and reliable self-report data from the patient." The FDA instead recommends the use of an observer-reported outcome (ObsRO) to assess patient behavior.[13] We note that only when the outcome measures are developed in collaboration with patients are the patients' voices reflected in the outcomes they are experiencing, whether those measures are reported by the patients themselves, observers, or proxies. We recommend that FDA include a discussion of the importance of including these patient voices through the development of outcome measures in the section on proxy-reported measures.

We appreciate the clear distinction and supporting rationale for the use of ObsRO measures, as well as the examples and implementation considerations provided in Appendix B. While we agree there are many instances where ObsROs are appropriate, we recognize there may be valid reasons a sponsor would use proxy-reported measures in the absence of available ObsRO measures or in the narrow circumstances when proxy-reported measures are preferable. Appendix B should therefore delineate these circumstances and provide sponsors with guidance on how to communicate to the FDA when they are using these measures. Circumstances in which proxy-reported outcomes may be appropriate might include tension between the patient and caregiver (e.g., impact on decision-making in the best interest of the patient), complex caregiver relationships (e.g., different caregivers for an individual patient resulting in inconsistent or inaccurate observation of patient), evolution of the patient-caregiver relationship (e.g., maturation of pediatric patient to adult and impact on timing for transition to a patient reported outcome from ObsRO).

For additional implementation considerations, we recommend review of the *Recommendations Report, Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An International Society for Pharmacoeconomics and Outcomes Research (ISPOR) COA Emerging Good Practices Task Force Report*,[14] developed by the ISPOR Task Force. The Task Force was comprised of a diverse cross section of the domestic and international research and regulatory community and charged with developing recommendations for addressing COA challenges in a clinical trial setting. Notably, the recommendations are based on the FDA's *Roadmap to Patient-Focused Outcome Measurement in Clinical Trials* (as included in this Draft Guidance). While the recommendations in this Report are focused on rare disease trials, the Task Force highlights the broader challenges with the FDA's approach to COA development and offers solutions which might be useful as the Agency finalizes the PFDD guidance series.[15]

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[13] In the Draft Guidance, the FDA describes ObsROs measures as "reports[…] from someone other than the patient or a health professional (e.g., a parent or caregiver) who has opportunity to observe the patient in everyday life. Useful when patients such as young children cannot reliably report for themselves, or to assess observable aspects related to patients' health (e.g., signs, 151 events, or behaviors)."

[14] Katy Benjamin Et. al., *Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report*, Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (2017).

[15] *Id.*

Digital Technologies to Collect COA Data

The FDA briefly discusses the increased use of digital health technology to collect responses from participants and caregivers, stating that sponsors "should define and provide rationale to justify the use of the DHT for measuring important feature(s) of the concept of interest in the target population." The use of digital technology and corresponding need to understand how technological innovation can minimize barriers to quality health care, especially for communities closest to injustice and inequity, is an issue of importance to the AAMC and the AAMC Center for Health Justice (https://www.aamchealthjustice.org/). To ensure stakeholders understand the impact of digital disparities in clinical trials, we strongly encourage the review of the White House Office of Science and Technology Policy *Community Connected Health Initiative* and related Request for Information on ways to strengthen community health through technology.[16]

Ensuring PFDD Guidance is Useful

We are optimistic that this tremendous undertaking will help "to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input" in agency decision-making.[17] It is important the PFDD guidance is accessible to *all* stakeholders, and it is equally important that the guidance can be practically applied. Given the detailed and complex nature of the PFDD guidance, we recommend the development of FAQs and other resources that would assist with implementation. We also recommend continued evaluation of the guidance once finalized.

We sincerely appreciate the opportunity to comment on this important endeavor and would be happy to work with the FDA in furtherance of any of the recommendations discussed in this letter, including bridging connections with our multi-sector partners and the FDA's Office of Patient Affairs. Please do not hesitate to reach out to me or my colleagues Daria Grayer (dgrayer@aamc.org) or Heather Pierce (hpierce@aamc.org).

Sincerely,

Ross E. McKinney, Jr., MD
Chief Scientific Officer

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

[16] AAMC Comments, *Request for Information on Strengthening Community Health Through Technology* (March 20, 2022), https://www.aamc.org/media/60171/download?attachment, see also: National Academies of Sciences, Engineering, and Medicine, COVID-19 and the Digital Divide: Implications for Policy and Equity, https://www.nationalacademies.org/event/03-03-2022/covid-19- and-the-digital-divide-implications-for-policy-and-equity#sectionEventMaterials (last visited, September 14, 2022).

[17] FDA Patient Focused Drug Development Guidance Series, https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical (last visited September 15, 2022).