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June 13, 2022

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Submitted via <https://www.regulations.gov>

Re: 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Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry [Docket No. FDA – 2021 – D – 0789]

The 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 comprise all 155 accredited U.S. and 16 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 employed 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. In 2022, the Association of Academic Health Centers and the Association of Academic Health Centers International merged into the AAMC, broadening the AAMC’s U.S. membership and expanding its reach to international academic health centers. Learn more at aamc.org.

The AAMC appreciates the FDA’s interest in the development of a *Race and Ethnicity Diversity Plan* (the “Plan”) to ensure that sponsors take meaningful steps to increase the enrollment of underrepresented populations in their clinical trials. The AAMC has long supported the FDA’s efforts to enhance diversity in clinical trials through participation in patient advisory committee meetings and responding to proposed guidance on patient engagement to inform FDA decision-making.¹

It is both a critical and opportune time for the FDA to address the underrepresentation of racial and ethnic populations in clinical trials, especially given the Administration’s current efforts to advance civil rights, racial justice, and equal opportunity across the Federal government (see, Executive Order (EO) 13985, *Advancing Racial Equity and Support for Underserved Communities Through Federal Government*).² In furtherance of these efforts, Federal agencies are taking active steps to “center[] equity in [their] programs, policies, and processes [...] changing the way [they] operate to ensure that government programs are within reach for all Americans—no matter their race, religion, color, national origin,

¹ AAMC Comments on *Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs*, Docket No. FDA-2019- D-1264 (August 2019), <https://www.aamc.org/media/11451/download>; Also see, AAMC Comments on *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input*, Docket. No. FDA-2018-D-1983 (September, 2018), <https://www.aamc.org/media/12326/download?attachment>.

² 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>. Also see, *Biden-Harris Administration Releases Agency Equity Action Plans to Advance Equity and Racial Justice Across the Federal Government* (April 14, 2022).

disability, sex, sexual orientation, locality, or age.”³ For example, the Department of Health and Human Services (HHS) recently joined 90 other Federal agencies in the release of an *Equity Action Plan*,⁴ and the Department’s efforts to advance opportunity and health equity do not end here. Last year, the HHS Secretary’s Advisory Committee on Human Research Protections (SACHRP) released recommendations on ways to promote “distributive justice in research” under the Federal Policy for the Protection of Human Subjects (also known as the “*Common Rule*,” 45 CFR part 46). SACHRP acknowledged, that while the systemic under representation of certain populations in research is a complicated issue, “[i]ssues of justice inspire demands for quick action, but it is far easier to identify problems than to craft meaningful and sustainable solutions.”⁵

Dismantling structural racism and addressing health inequity is a primary concern for the biomedical research and broader community, particularly in light of the persistent racial violence and social tensions that have disproportionately affected people from racial and ethnic minority groups. **The AAMC and the AAMC Center for Health Justice (www.aamc.org/healthjustice)⁶ agree that addressing the underrepresentation of populations in research is a complex issue that requires immediate action. To achieve this goal, we recommend any diversity strategy or Plan to improve the enrollment of underrepresented racial and ethnic groups in clinical trials include robust coordination and engagement with individuals and communities that are closest to injustice and inequity (see *Section II. Community Engagement*).**

I. Inter-Agency Coordination

In previous comments to the FDA, the AAMC has recommended the use of the FDA’s Office of Patient Affairs (OPA) for streamlining patient engagement efforts and ensuring a coordinated and broader inter-agency approach.⁷ Considering the current agenda to address equity and justice across the Federal government, **we strongly recommend the immediate establishment of an inter-agency working group or task force to enhance collaboration and facilitate comprehensive evaluation of the FDA’s patient engagement efforts, including activities related to this proposed guidance such as the related collection of race and ethnicity data, and social determinants of health data to better understand the retention of participants in studies.** The FDA should consider utilizing the existing infrastructure and resources of the OPA — established, in part, to coordinate and implement FDA’s patient engagement activities and serve as a platform for communicating with the patient community.⁸

There are two key resources that might be of interest if the FDA proceeds with the establishment of an interagency working group — first, the *Interagency Working Group on Equitable Data* (“Data Working Group”) supported by EO 13985 and second, April 2022 recommendations from the National Academies of Science, Engineering, and Medicine (“Academies”) on *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*.

³ Press Release, *HHS Statements on New Plan to Advance Equity in the Delivery of Health and Human Services* (April 14, 2022).

⁴ Department of Health and Human Services, *Equity Action Plan* (last visited June 7, 2022).

⁵ Department of Health and Human Services, Secretary’s Advisory Committee on Human Research Protections, *Consideration of the Principle of Justice under 45 CFR part 46* (July 22, 2021).

⁶ The AAMC Center for Health Justice was founded in 2021 with the primary goal for all communities to have an equitable opportunity to thrive — a goal that reaches well beyond medical care. Achieving health justice means addressing the common roots of injustice through implementation of policies and practices that are explicitly oriented toward equity. The AAMC Center for Health Justice partners with public health and community-based organizations, government and health care entities, the private sector, community leaders, and community members to build a case for health justice through research, analysis, and expertise. Additional information available at www.aamc.org/healthjustice.

⁷ *Supra* Note 1.

⁸ Request for Comment, *Enhancing Patient Engagement Efforts Across the Food and Drug Administration*, Docket No. FDA-2017-N-0455 (March 2017).

Pursuant to EO 13985, the Data Working Group was created to facilitate the sharing of information and best practices across the Federal government and develop recommendations for addressing inadequacies and inequities in federal data collection programs. **Notably, the Data Working Group recently issued a recommendations report which identified several priority areas, one of which has tremendous impact on this proposed guidance: the revision of the Office of Management and Budget (OMB) Statistical Policy Directive 15: *Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity* (an issue further discussed below, Section V. Definition of Race and Ethnicity). The need for revision was clearly articulated by the Data Working Group in the final report:**

“Federal standards are important because they ensure consistent and comparable data government-wide. However, many who met with the Working Group emphatically stated that many individuals—for example, people of Middle Eastern and North African heritage and subgroups of Asian American, Native Hawaiian and Pacific Islanders—are not represented within the current minimum racial and ethnic categories, leaving them unseen in government statistics and masking important inequities.”⁹

The FDA should also refer to the recent Academies publication on improving representation in clinical trials, recommending the establishment of an interdepartmental working group that includes HHS/FDA. This group would be responsible for completing specific tasks such as “determining what ‘representativeness’ means for [clinical trial] protocols and product development plans.”¹⁰ As stated in the Report:

“The Department of Health and Human Services (HHS) should establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies, including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), Health Resources Services Administration (HRSA), Indian Health Services (IHS), Centers for Medicare and Medicaid Services (CMS), and two departments outside of HHS, the Department of Veterans Affairs and Department of Defense.”¹¹

II. Community Engagement

The FDA’s proposed Plan supplements previous guidance, the *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016) which recommends sponsors develop and submit a plan to increase participant diversity in clinical trials. The AAMC has commented extensively on the collection and use of race and ethnicity in clinical trials, emphasizing the need for robust bi-directional community and patient engagement to maximize the recruitment and retention of diverse populations.¹² Several of those recommendations are applicable here:

- Identify effective communication pathways to reach diverse patient populations such as increasing access to telehealth services and electronic technology.

⁹ Equitable Data Working Group Report, *A Vision for Equitable Data Recommendations from the Equitable Data Working Group*, Page 5 (April 22, 2022).

¹⁰ National Academies of Sciences, Engineering, and Medicine 2022. *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/26479>.

¹¹ *Id.*

¹² AAMC Comments, *Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies*; Docket No. FDA-2016-D-0734 (September 2016).

- Engage minority professional health organizations, community partners, and advocacy groups to build authentic relationships between the FDA, sponsors, and interested communities, including racial and ethnic subpopulations or populations with low literacy or limited English proficiency.
- Ensure community partners are not solely advocates selected, trained, or funded by drug device and biotechnology companies. Partnerships should be led by local organizations and leaders who are better positioned to leverage existing relationships, ensuring that recruitment is conducted in a culturally sensitive manner while upholding public trust.
- Establish a definition for successful patient enrollment and participation. “An ideal outcome should not only include an end result of medical products which meet the needs of a diverse patient population, but also the development of a broad community of patients who are active participants in medical product development. This will in turn facilitate dissemination efforts and outreach to populations that would benefit from information about those medical products.”¹³ An ‘ideal outcome’ also extends to the *use* of newly generalizable evidence and strengthened community relationships to ensure all populations have equitable access to the medical innovations developed through clinical research.

Referencing the *Tuskegee Study of Untreated Syphilis in the Negro Male*, the FDA states that the “mistrust of the clinical research system may stem from historical events that adversely impacted racial and ethnic minorities” (lines 109-111). **In recognition of historical and contemporary events and the continued mistrust in the health care system,¹⁴ it is imperative that the FDA encourage sponsors to solicit community input to assist not only with their enrollment and recruitment efforts but the development of the Diversity Plan itself. Further, it is notable that the Plan does not include a specific recommendation for community co-development¹⁵ which we believe could be added as additional Category or incorporated into Category 3 (Goals for enrollment of underrepresented and ethnic participants) or Category 4 (Specific plan of action to enroll and retain diverse participants).**

III. Content of Plan and Additional Issues for Consideration

Plan Content and Clarification of Goals

In *Section V., Content of the Plan*, the FDA identifies several issues that sponsors should consider, including “defin[ing] enrollment goals for underrepresented racial and ethnic participants *as early as practicable* in clinical development for a given indication” (emphasis added). The FDA also asserts that “[i]n the event that recruitment goals are not met despite best efforts, sponsors should discuss with FDA a plan to collect this data in the post-marketing setting” (footnote 24). On its face, these recommendations appear to provide sponsors with significant flexibility to self-define goals and/or standards for the assessment of race and ethnicity without specific guidance on ideal benchmarks and/or goals for enrollment and retention.

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.

¹³ *Id.*

¹⁴ Shariff et al., More than Tuskegee: Understanding Mistrust about Research Participation J Health Care Poor Underserved. 2010 August; 21(3): 879–897. doi:10.1353/hpu.0.0323.

¹⁵ The FDA should consider the White House Office of Science and Technology Policy’s current activities related to the co-production of knowledge with communities to inform Federal research programs, see: <https://www.nationalacademies.org/event/05-12-2022/co-producing-knowledge-with-communities-equity-in-federal-research-programs> (last visited June 7, 2022).

Additional Issues and Topics for Inclusion

There are several aspects of the Plan that could benefit from greater detail and supplementary guidance to ensure sponsors clearly understand the FDA’s expectations, thereby minimizing the potential for ambiguity and misunderstanding. Additionally, there are issues and topics that should be considered but are not explicitly identified or expanded in the draft guidance. These include but are not limited to:

- Compensation to research participants and caregivers/family members
- Financial and social burden related to participation in clinical trials
- Language and literacy barriers
- Access to telecommunication services
- Building inclusivity in clinical trials for pregnant and lactating women, pediatrics, individuals with disabilities, LGBTQ+ communities and others underrepresented groups
- Institutional review board (IRB) considerations (e.g., ensuring diverse representation of IRB membership, IRB determination of clinical trial representation)
- FDA review of sponsor data from outside of the United States

We encourage the FDA to reinforce this guidance with supplemental information or guidance addressing the issues above, in addition to giving deference to the potential issues and concerns raised by other commentors.

IV. Timeline for Submission

The FDA indicates that sponsors should “collect data to explore the potential for differences in safety and/or effectiveness associated with race and ethnicity throughout the entire development life-cycle of the medical product and just during pivotal trials(s) or studies” (lines 208-211). Additionally, sponsors should submit their Plan “as soon as practicable during drug development but no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often at the EOP2 meeting)” (lines 150-152).

To ensure potential differences in safety and/or effectiveness are addressed “throughout the *entire* development lifecycle” (emphasis added), we recommend sponsors submit their Plan to the FDA well in advance of the formal End-of-Phase 2A (EOP2) meeting. EOP2 meetings are intended to “address outstanding questions and scientific issues that arise during the course of a clinical investigation, aid in the resolution of problems, and facilitate evaluation of drugs.”¹⁶ Conceivably, for safety and efficacy issues to be prudently addressed, concerns should be discussed and evaluated *at the time of* Plan development (i.e., prior to the EOP2 meeting).

V. Definition of Race and Ethnicity

Race and Ethnicity as Dynamic Constructs

Finally, we would like to emphasize that race and ethnic identification are dynamic rather than static constructs and note the FDA’s reliance on the OMB’s definition of race and ethnicity in the draft guidance.¹⁷ The AAMC provided comments on the OMB’s 2016 request for feedback on

¹⁶ Department of Health and Human Services and Food and Drug Administration, Guidance for Industry: *IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information* (May 2021).

¹⁷ See Footnote 3, “FDA follows the Office of Management and Budget’s definitions of race and ethnicity. See Office of Management and Budget (OMB) Directive No. 15 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity (October 30, 1997). [...] Consistent with OMB Policy Directive 15, the categories in this classification are social-political constructs and should not be interpreted as being scientific or anthropological in nature. Ethnicity is comprised of two

Maintaining, Collecting, and Presenting Federal data on Race and Ethnicity, and reiterated many of those recommendations in response to a 2021 OMB request for comments on advancing equity across the federal government. Four recommendations are especially applicable to this draft guidance:¹⁸

- Abandon the “principal minority race” category currently in use and reserved for “Black or African Americans.” The continued use of the category permits in certain circumstances the presentation of the “White” category, the “Black / African American” category, and an “All other races” category. Significant differences might, however, exist between groups aggregated into the “All other races” category (i.e. Asian Americans, Native Americans, Hispanics/Latinos, etc.), thereby impeding our ability to identify salient inequities. In service of detecting subgroup differences with the aim of developing needed interventions, use of “All other races” as a reporting category should be discontinued in instances where the sample sizes of racial/ethnic subgroups permit more detailed reporting.
- The collection of race and ethnicity information should include the collection of additional demographic data to capture groups that are often excluded from definitions related to “health equity/health disparity” (i.e., LGBTQ+, persons with disabilities).
- The minimum set of racial and ethnic categories used when collecting or presenting data *should not* limit the collection of additional, more granular race or ethnicity data, provided any subgroup can be aggregated into the minimum set when required.
- The creation of a subcategory for individuals who self-identify as Middle Eastern/North American (MENA), a group often aggregated into the “White” race category, is critical to ensuring the accurate collection of disparities germane to MENA and other groups. Equally important, is that any effort to refine the OMB’s racial and ethnic categories, must be rooted in community guidance. Self-identified race and ethnicity must remain the gold standard and every effort must be made to ensure all populations can “see” themselves in the response categories.

While the AAMC supports the collection of race and ethnicity data, it is critical to note that the OMB’s guiding principles have not been updated since the initial 1977 standards and subsequent 1997 revision. Reliance on the OMB’s antiquated terminology related to race and ethnicity in the context of drug/device product performance, increases the potential for bias and discrimination.¹⁹ It also undermines the intended goals of this proposed guidance and ultimately the broader goals outlined in the HHS Equity Action Plan. We recommend consideration of the recommendations issued by the White House Interagency Data Working Group, as well as coordination with the OMB’s current efforts to develop updated guidance to promote an “improved understanding” of racial and ethnic classification categories.²⁰

We would also like to re-emphasize the aforementioned recommendation for a multi-stakeholder convening to discuss the Federal collection and use of demographic information, standardization of data categories, and discontinuation of categories that further perpetuate salient inequities and discrimination, (see Section I).

categories: Hispanic/Latino or not Hispanic/Latino. Race is comprised of five minimum categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White.”

¹⁸ AAMC Comments, *Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity*, Docket No. OMB 2016-23672, <https://www.aamc.org/media/11646/download?attachment> (October 2016).

¹⁹ For example, the FDA requests sponsors collect data on factors for device performance (e.g., phenotypic, anatomical, or biological) to understand effects across diverse populations, using variations skin pigmentation that impact device performance (lines 184-188).

²⁰ Supra Note 9.

Consideration for Other Factors and Determinants of Health

The FDA recommends that a Plan should “[e]nroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, such as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other persons of color, in clinical trials.” Citing the White House *National Strategy on Gender and Equality*, the FDA also advises sponsors “to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.”

In the AAMC’s comments to the OMB on the collection of race and ethnicity data, we note that “demographic data are a starting point for a comprehensive data collection system and that national efforts must include that capture of individual-level social need data (e.g., homelessness, food insecurity, etc.) and community/area-level social determinant data (availability of affordable housing, food desert status, etc.), factors that are amenable to intervention in ways that demographics are not.”²¹ **We appreciate the FDA’s recognition of the impact of factors and determinants beyond race and ethnicity and suggest the FDA consider *additional factors and determinants, including the intersection of under-acknowledged determinants that impact individuals in underserved communities (e.g., racism and discrimination, climate, housing, education, food security, genetic predisposition, geographic considerations).***²²

We sincerely appreciate the opportunity to comment on such an important endeavor, and one that is taking place at a time when there is extraordinary interest in the promotion of health equity and justice. The AAMC and the AAMC Center for Health Justice have extensive multi-sector relationships with organizations and community leaders, many of whom would be eager to assist the FDA with these efforts. We 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. 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

²¹ Supra Note 18.

²² The NIH National Center for Complementary and Integrative Health (NCCIH) is currently soliciting public comment on defining key factors and determinants that contribute to “whole person health” (i.e., “factors that can influence health either positively or negatively, and that encompass the full continuum of biological, behavioral, social, and environmental domains”). NCCIH plans to develop a comprehensive list of common determinants that can be used in research and patient care. See, Request for Information (RFI): *Identification of a Set of Determinants for Whole Person Health* (NOT-AT-22-019).