September 25, 2024

Re: **Docket No. FDA–2021–D–0789**
Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration's ("FDA's" or "the Agency's") Draft Guidance for industry entitled, *"Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies: Draft Guidance for Industry.* Guidance on this topic is both timely and crucial for stakeholders across the clinical research enterprise.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1] We focus here on information that would be helpful for the understanding of healthcare, health disparities, and clinical research

The MRCT Center supports the FDA and the Department of Health and Human Services' continued commitment to enhance diversity and representation across clinical research and the development of the Draft Guidance in particular. We appreciate that the Draft Guidance is concise and easy to follow. Nevertheless, additional detail would be very helpful for organizations working to operationalize this guidance.

Comments

I. Introduction

- Recommendation to include further detail, feedback, and accountability mechanisms for sponsors to ensure compliance and effectiveness of Diversity Action Plans (DAPs).

> "*In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory*

[1] Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, and Harvard University.

> *requirements are cited. The use of the word should in Agency guidance's means that something is suggested or recommended, but not required. An exception to this framework derives from the requirement in section 3601 of FDORA for FDA to specify in guidance, the form and manner for the submission of Diversity Action Plans. Accordingly, insofar as section VII of this document specifies the form and manner for submission of a Diversity Action plan, it will have binding effect, once this guidance is finalized, as indicated by the use of the words, must, shall, or required." [Page 2-3, Lines 65-75]*

The FDA's draft guidance DAP is an important move toward enhancing diversity and inclusion in clinical research. Although this guidance offers recommendations rather than rules, Section 3601 of FDORA requires the FDA to establish clear, binding procedures for submitting DAPs once the guidance is finalized. To make this guidance more effective and ensure DAPs are properly implemented, we suggest adding mechanisms for feedback and accountability.

Currently, FDA's draft guidance states that, "*Depending on the specifics for each clinical development program, the relevant Division 489 in CDER or CBER may or may not provide feedback on the Diversity Action Plan.*" It is difficult, however, to know whether the plan is or is not acceptable without acknowledging receipt and providing a timeline for response. We encourage FDA to specify that no feedback equates to FDA having no major issues with the DAP submission. Furthermore, FDA should provide feedback to sponsor if it is explicitly requested by the sponsor within a given period of time. This approach preserves FDA flexibility not to comment on every DAP submitted while ensuring major issues and sponsor questions are addressed. In any event, FDA should establish a formal feedback process that allows sponsors to receive timely evaluations of and recommendations to their submitted DAPs, with a go/revise/no-go decision. This feedback should be provided within a set timeframe to ensure that sponsors have ample opportunity to refine their plans in response to regulatory expectations.

More importantly, the Draft Guidance does not outline what would be acceptable diversity goals; there are no anticipated goals to which to aspire. Of course, realistic goals will be dependent on a number of factors, and we encourage the final guidance to enumerate those factors and how FDA will evaluate them. Despite best good-faith efforts, DAP goals may be missed for a given demographic group. We request FDA outline the expectations for meeting the DAP (e.g., within what percentage of DAP goal?) and how the significance of over or under-enrollment of certain populations will be evaluated. How will "failure" be defined, and what will be the consequences of missing those goals? We encourage FDA to focus on those situations where missed goals may lead to an inability to identify a serious risk, a failure of expected pharmacological action or efficacy, or other key aspects of a medical product's profile. FDA retains significant authority to enforce DAP compliance through postmarket mechanisms (e.g., postmarketing requirements and postmarketing commitments) (https://www.fda.gov/media/170899/download). We encourage FDA to finalize that draft guidance expeditiously.

Smith Center #771, 1350 Massachusetts Ave, Cambridge, MA 02138 75 Francis Street, Boston, MA 02115
Tel: 617-827-7413 | Email: bbierer@bwh.harvard.edu www.MRCTCenter.org

In our opinion, further guidance could be provided in Appendix 1 related to the detail anticipated for *"a description of the enrollment and retention strategies for the study population."* In the absence of direction, the tendency will be to minimize specificity both to allow flexibility and to decrease the number of revisions to the DAP plans required. However, in the absence of some detail, it is unclear how FDA will evaluate these plans nor how it can learn from the accumulation of experience over time.

To improve accountability and clarity in decision-making, we encourage FDA to introduce transparent guidelines for how DAPs will be assessed. The criteria for evaluation could focus on several key areas. First, site selection should be clearly defined and documented, reflecting the value that the study process and findings are anticipated to bring to local communities and encompassing sustainable commitment to the target region and country (potentially inclusive of post-trial and market access). In that section, the history of direct engagement not only with the site but with the local community should be evaluated. The criteria may also evaluate how well the DAP has described the mechanisms for local communities, particularly disadvantaged groups, to shape and provide feedback on the organization's engagement, choice of study question, planned study design and conduct, DEI planning, and the development of the informed consent document and other participant-facing materials. At each annual review, FDA should evaluate feedback from the community, including execution of study conduct and return of results. Additionally, the FDA may assess the measures that organizations plan to take and then have taken to address local needs and priorities.

To ensure sponsors meet their diversity targets, the FDA could set quantifiable standards for monitoring DAPs. Suggested metrics include *diversity enrollment rates*, which measure the percentage of underrepresented groups compared to the targets set in the DAP; *enrollment rate variability,* which analyzes differences in enrollment rates among various demographic groups throughout the trial phases; and *retention rates*, which track the retention of participants from diverse backgrounds throughout the study.

III. **Clinical Studies Requiring Diversity Action Plans**

- Recommendations for Requiring Diversity Action Plans for All Phase 3 Clinical Trials

  For drugs, a Diversity Action Plan is required for a clinical investigation of a new drug that is a phase 3 study (as defined in 21 CFR 312.21), or as appropriate, another pivotal clinical study of a drug (other than a bioavailability or bioequivalence study). [Page 6, Lines147-149]

The FDA's current guidance specifies that a DAP is mandatory for Phase 3 clinical trials of new drugs, as defined under 21 CFR 312.21, and other pivotal studies involving new drugs, excluding bioavailability or bioequivalence studies. This requirement reflects a significant step towards ensuring that clinical research includes diverse populations and addresses various demographic factors that may affect drug efficacy and safety.

However, the guidance does not explicitly clarify whether DAPs are also required for Phase 3 trials of non-innovative or previously approved products that are in the market. This ambiguity could lead to inconsistencies in how diversity is addressed across different types of clinical trials. In the trials that led to the approval of these products prior to the attention to diversity and representativeness, few data were available. New Phase 3 trials of non-innovative or previously approved products that are in the market provide an opportunity to correct this deficiency. Planning a clinical study with the representativeness of the intended population in mind is not a consideration limited to new products.

To promote greater inclusivity and consistency in clinical research, we recommend that the FDA extend the requirement for DAPs to all Phase 3 clinical trials, regardless of whether the drug is new or previously approved.

A. Enrollment Goals

- Recommendation for disaggregating US enrollment goals from global clinical trials

  Generally, enrollment goals should be informed by the estimated prevalence or incidence of the disease or condition in the U.S. intended use population for which the medical product is being studied [Page 8, Lines 232-235].

  FDA recognizes the importance of global medical product development and supports the use of well-designed and conducted multi-regional clinical studies, when appropriate, to provide the evidence of safety and effectiveness for FDA-regulated medical products. Globally conducted clinical development programs should be designed with appropriate consideration given to differences in disease characteristics, medical practice, and available therapies when selecting foreign clinical sites and defining geographic regions. A Diversity Action Plan for a multi- national clinical study must describe participant enrollment goals for the entire study and should not be limited to U.S.-enrolled participants. Additionally, the overall study design, including the selection of study sites, should account for the need to enroll a population representative of the U.S. intended use population as part of the overall medical product development program. [Page 10, Lines 295-31].

The draft guidance suggests that enrollment goals should be based on the estimated prevalence or incidence of the disease or condition in the U.S. intended use population, which is consistent with FDA's jurisdiction and scope of responsibilities. However, as noted, clinical trials are often conducted globally, and drugs are ultimately marketed to, and used by, populations around the world. The draft guidance acknowledges that a DAP for multi-national clinical studies must include participant enrollment goals for the entire study, not just for U.S.-enrolled participants. The guidance also underscores the importance of ensuring that the overall study design and site selection process reflect the U.S. intended use population. This dual focus can create confusion about how to balance diversity targets based on US demographics with the reality of differing

demographic profiles, differing definitions for demographic categories, and differing research priorities and context-specific needs in countries outside the US.

We recommend that the guidance explicitly differentiate between U.S. race/ethnicity goals and those for participants from non-U.S. regions. Applying U.S. demographic standards globally could inadvertently create inequalities, both in the US and in other countries, if participants from other countries are used to "meet" U.S. demographic targets. Enrolling participants in Africa who would be categorized as Black, or in Latin America who would be categorized as Hispanic, for example, does not contribute to the "social" goal of reducing barriers to support better inclusion of African or Hispanic Americans within the USA. Further, while race/ethnicity have been used as proxies for the "biological" goal of predicting variability in response to medications (assuming differences in genetics, discrimination, stress, diet, and access to medical care experienced by people of different races/ethnicities), using race/ethnicity as a proxy for biology becomes increasingly meaningless with changes in context. A Korean person born and living in Korea can't be "substituted" for an American person of Korean descent born and living in California, even though both may be labeled as "Asian" in demographic profiles.

That said, there should be flexibility to augment US data with ex-US data where the sponsor can demonstrate that the ex-US patient is comparable to the US patient with regards to patient-related factors, disease-related factors (e.g., prevalence, molecular drivers), healthcare-related factors (e.g., access to similar standard-of-care interventions), and other factors (e.g., social determinants of health). The burden rests on sponsors to justify equivalence between ex-US and US patients, and that justification should be evaluated by FDA.

As medical practitioners, it is incumbent upon the research community to first 'do no harm' in our recruitment practices. Tackling the socio-economic and other barriers that prevent populations from taking part in research requires prioritization of sustained engagement with community groups, researchers, sites, and national authorities in planning for trials and defining goals. That remains the case whether those entities are in the US or in other countries where trials are being planned and conducted. To address this issue, the guidance should provide clearer instructions on how U.S. enrollment diversity goals should be considered within the broader context of global trials. It would be beneficial if the guidance clearly stated whether and with what detail sponsors are anticipated to identify the regions and/or countries involved in their trials and document their diversity strategies for those regions and or/countries.

Site selection and recruitment should follow purposeful engagement in the local and regional culture, considering the needs of the local population, and proceed only if the trial is responsive to those needs. We recommend that FDA be explicit about the criteria they will be using to review the enrollment goals, site capacity profiles, recruitment and retention plans, and risk and contingency management plans in the submitted DAPs and whether those criteria will be the same for studies in the US and/or outside the US.

B. Rationale for Enrollment Goals

- Comprehensive Diversity Action Plan strategy across a clinical trial program

> *If a sponsor plans to conduct several clinical studies to support a single marketing submission, the sponsor may opt to specify enrollment goals across the planned clinical studies. A sponsor's rationale for having different enrollment goals across planned studies must be included in the Diversity Action Plan; the rationale provided should indicate how individual clinical studies are intended to contribute to the overall enrollment goals for the clinical development program for the medical product (i.e., for a particular indication or intended use). [Page12, Lines* 343-349]
>
> FDA's recommendation for sponsors to develop and implement a comprehensive diversity strategy across their entire clinical development program, including early studies when possible, is a commendable step towards more inclusive clinical research.

By integrating diversity considerations from the outset, this approach ensures that enrollment goals are in alignment with the overarching objectives of the clinical program. Notably, if a sponsor plans to conduct multiple clinical studies for a single marketing submission, they may specify enrollment goals for each study. However, they must provide a rationale in their DAP for any variations in these goals. This rationale should explain how each study contributes to the overall diversity objectives for the medical product, considering its intended use or indication.

To enhance the effectiveness of this comprehensive approach, some general recommendations are presented here. First, FDA should offer examples of what constitutes an acceptable rationale for varying enrollment goals across different clinical studies. Providing clear criteria for acceptable rationales will help sponsors develop robust diversity strategies and ensure that any variations in enrollment goals are well-founded and aligned with the program's diversity objectives.

Additionally, FDA should consider whether structuring DAPs at a higher level than individual studies might be more efficient and practical. For example, structuring DAPs at the level of the indication or specific conditions could offer a more comprehensive and strategic approach to diversity. Guidance on such higher-level structuring would help sponsors align their diversity efforts across multiple studies and address the needs of diverse populations more systematically.

Finally, to improve recruitment of diverse populations, FDA could encourage the inclusion of a broader range of trial sites, particularly those that have not been previously utilized or been underutilized but have access to diverse populations. Relying on the same trial sites repeatedly limits the diversity of the participant pool. By expanding the network of trial sites and incorporating new, diverse locations, sponsors can enhance their ability to recruit a more representative sample of participants.

Overall Comments

- Update reporting expectations for race and ethnicity in the US

  FDA should take this opportunity to clarify whether demographics regarding race and ethnicity should be reported according to the categories defined in FDA guidance (Footnote 78) or according to the OMB revisions published in March 2024 ("Revisions to Statistical Policy Directive No. 15: Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity.") While adopting this standard reporting requirement may or may not be required (and will not resolve global complexity), it seems that having one standard set of reporting categories for the US will be helpful. At a minimum, it will allow data collection of population demographics in research to align with those in other federal data (e.g., US Census Data and others).

- Addressing Challenges with Global Data Collection in Clinical Trials

  Global clinical trials face significant challenges due to the variability in definitions of race and ethnicity across different countries. The FDA, for instance, relies on definitions and categories set by the Office of Management and Budget (OMB) some time ago that are specific to the U.S. and do not have universal standards. This lack of uniformity complicates the collection and analysis of race and ethnicity data in multinational studies, making it difficult to achieve meaningful and comparable results across diverse populations.

  Another major issue is the legal restrictions imposed by many countries on the collection of certain types of personal information. For example, privacy laws in countries such as France and Germany impose strict limits on collecting sensitive demographic information such as race and ethnicity. These regulations can impede the accurate reporting and analysis of such data in multi-regional clinical trials, making it difficult to achieve a comprehensive understanding of how medical products perform across different populations.

  To address these issues, a few steps can be taken. First, FDA should acknowledge that definitions of race and ethnicity vary widely around the world.[2] Second, as previously mentioned, the health experiences of individuals born and living outside the U.S. can differ significantly those of people who have been in the U.S. for many years (or generations), but who may be grouped together

[2] Working with international organizations like the UN and WHO and national agencies such as the CDC could help standardize how demographic data is defined (or mapped to a given standard), collected, and analyzed in health surveys. Although achieving standardization will take time, recognizing and addressing these differences is crucial.

under the same umbrella racial category (e.g., "Black" or "Asian"). It's important to separate U.S. data from global data, potentially disaggregated data for U.S. participants and for participants outside the U.S. by region (rolling up to an ex-US grouping).[3] U.S.-specific data can then more accurately reflect the unique characteristics of American populations and the level of access to and participation in trials in the U.S., while global data can be used to complement and enrich the overall analysis of safety and efficacy.

Efforts to collect data from diverse populations should continue even if initial attempts are unsuccessful or lack statistical feasibility. Reporting could include disaggregated data that can be pooled for thorough analysis. When trial size allows, applying a Bayesian approach can help identify differences between US and non-US participants, and decisions on further data collection, analysis, and reporting. Ensuring robust representation is critical for both social justice and scientific accuracy.

- Structure of the Guidance

The June 2024 draft guidance on the DAP is notably concise, focusing primarily on enrollment goals and strategies for recruiting and retaining diverse patient populations. The June 2024 draft guidance contrasts with the April 2022 draft guidance, which provided a more comprehensive structure. The earlier draft included a detailed framework beginning with an epidemiological overview, assessing disease prevalence, scoping the medical product development program, setting enrollment goals, and outlining specific action plans for diverse patient enrollment and retention.

The previous draft's more detailed structure offered a valuable roadmap for organizations, guiding them through the processes that are necessary prior to developing effective enrollment goals. It started with an epidemiological overview to understand the disease landscape, followed by a scoping of the medical product development program to align diversity goals with overall research objectives. This logical approach was instrumental in helping organizations to systematically develop strategic diversity programs that were both comprehensive and aligned with regulatory expectations.

To enhance the final guidance, we recommend reinstating a similar structure[4] as outlined in the April 2022 draft. Incorporating a detailed framework that begins with an epidemiological overview and progresses through the various stages of medical product development will provide organizations with a clearer outline for developing and implementing effective diversity strategies. This structured approach will help ensure that diversity goals are not only set but are also grounded in a thorough understanding of disease prevalence and product development needs.

[3] Allowing for the possibility that the sponsor may demonstrate comparability between global data and that collected in the US.

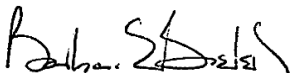
[4] The expanded structure could be included either within the guidance itself or as an Appendix.

By including detailed pointers and guidance on each of these stages, the final guidance will offer valuable support for organizations aiming to create and maintain strategic diversity programs in line with regulatory expectations.

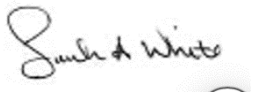
The MRCT Center is grateful for the opportunity to review and comment on this Draft Guidance document. We remain supportive of efforts to improve how Diversity Action Plans are developed, submitted, and utilized. We welcome any opportunities to discuss.

Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu or sawhite@bwh.harvard.edu if we can be helpful or if you wish to discuss.

Respectfully submitted,



Barbara E Bierer, MD
Faculty Director, MRCT Center



Sarah A White, MPH
Executive Director, MRCT Center