Brigham and Women's Hospital
Founding Member, Mass General Brigham

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

May 31, 2022

Lola Fashoyin-Aje, MD
Deputy Division Director & Assoc. Dir, Science & Policy to Address Disparities
Oncology Center of Excellence
Center for Drug Evaluation and Research (HFD–150)
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993–0002

Submitted at *https://www.regulations.gov*

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Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry

Dear Dr. Fashoyin-Aje,

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 (FDA)'s request for input on its draft, "*Diversity Plans To Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry,*" published in the Federal Register on Thursday, April 14, 2022. It is a timely and important draft guidance.

The MRCT Center is a research and policy center that addresses 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. In addition to other initiatives, over the last six years, the MRCT Center has been intimately involved in advancing diversity, equity, and inclusion (DEI) in clinical trials. We initiated and executed the initial part of this work in collaboration with FDA Office of Minority Health and Health Equity (OMHHE), but please note that we have not discussed the comments provided herein with anyone in OMHHE or more broadly at FDA. 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]

Particularly in this time of heightened awareness of structural and systemic racial prejudices and health inequities, the draft guidance requiring diversity plans to improve enrollment from underrepresented racial and ethnic populations in clinical trials could not be more important or timely. The MRCT Center applauds FDA's direct attention to measures that will help to ensure that clinical trials leading to regulatory review and approval are sufficiently and appropriately diverse. The submission of a prospective and timely Race and Ethnicity Diversity Plan, reviewed by FDA, is one appropriate mechanism. We appreciate that the mission of FDA, at least in part, is the evaluation of efficacy and

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safety of medical products that make claims about health; in this context, an understanding of biologic variability in diverse populations is properly regarded as one core mission of FDA. Evidence-based conclusions about safety and efficacy can only be made by collecting and analyzing robust data that examine the heterogeneity of effect in diverse populations. Increasing the diversity of individuals participating in clinical trials is not only important for the understanding of biology, but also to address health disparities and to promote public trust.

In the context of support for the recommendations proposed by FDA, we offer a few additional comments for consideration.

A. Specifics of the Race and Ethnicity Diversity Plan

Section V describing the content of the Race and Ethnicity Diversity Plan is helpful in its specificity and comprehensiveness. A number of further clarifications would be helpful.

1. Baseline demographic data

Given that the correlation of product performance with race and ethnicity has not been a central focus of product development to date, baseline data to set enrollment goals are likely inadequate. Reliance on the epidemiology of the disease is helpful, but unlikely to permit informative statistical analyses by race or ethnicity. In the absence of affirmative (e.g., known metabolic differences) or likely (e.g., skin pigmentation) evidence of differences, it would be helpful for FDA to outline if there are other assessments that sponsors would be expected to collect (e.g., pharmacokinetic, pharmacodynamic, and/or pharmacogenomic data by race and by ethnicity.)

FDA mentions utilization of "various data sources (e.g., published literature and real-world data) to set enrollment goals" (line 216-217). It would be helpful to have more clarity around use of real-world data (RWD), such as which databases FDA recommends or prefers and how to transcribe RWD for reliable racial and ethnic categories recommended for tracking. Since the published literature may be biased, and RWD may not be fit-for-purpose, it would be helpful to know if FDA considers minimum enrollment goals such as the demographics of the overall population with the disease to be sufficient. In other words, if there is evidence of differences, sponsors should strive to assess those differences in the applicable pivotal trials; in the absence of data, sponsors should consider enrollment in the trial that mirrors the epidemiology of the disease in the U.S.

2. Timeline

It is important for FDA to emphasize that attention to inclusion of diverse populations is essential throughout the lifecycle of product development as is developing ancillary data that will inform potential differences by race or ethnicity (e.g., pharmacokinetic, pharmacodynamic, or pharmacogenomic data). It appears somewhat inconsistent that the Plan is anticipated to "outline the sponsor's plan to 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 not just during the pivotal trial(s) or studies," (lines 208-211) and yet sponsors are directed to submit the Plan to FDA "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). Arguably, and particularly if there is concern for differences in product performance based on factors associated with race and ethnicity, the Plan should be submitted earlier than EOP2; while sponsors are developing their diversity plans, FDA should encourage early consultation with

the Agency. Additionally, FDA's formal meeting guidance does not address the discussion of the Race and Ethnicity Diversity Plan as an independent reason to request a meeting. We recommend that FDA review the Formal Meetings guidance to align with this draft guidance to include consideration of discussion of the Plan as an appropriate reason to request a meeting.

3. Clinical trial data from outside the U.S.

Many applicable pivotal trials are conducted as multi-regional clinical trials (MRCTs) with participants from outside the U.S. Will FDA provide guidance for racial and ethnic categories for participants enrolled outside of the U.S. and in MRCTs, and how will FDA review the contribution of data collected outside the U.S. to the overall Race and Ethnicity Diversity Plan?

B. Definitions of race and ethnicity

The MRCT Center appreciates that FDA follows the directive of the Office of Management and Budget (OMB) in the definitions of race and ethnicity. These definitions date from 1997 and have not been updated since; they no longer resonate with the U.S. population, nor with concepts of race and ethnicity outside the U.S. Multi-racial and multi-ethnic backgrounds and ancestry are common; and differences in ancestry are likely more important, and more nuanced, than the five racial and two ethnic categories designated by OMB Directive No 15.[2] Since clinical trial data are often multinational, we encourage FDA to work with OMB, other health regulatory authorities, other stakeholders, and, importantly, the diverse public to establish terms that will resonate with the U.S. (and external to U.S.) populations.

While this suggestion may appear to be outside the scope of the draft guidance upon which we are asked to comment, it is important and has direct impact on any sponsor's proposed Plan. If clinical trialists will be collecting personal information from participants as a routine part of data collection, the choice of categories and the methods of soliciting the information should resonate with —and not offend or further alienate—the people with whom we engage.

C. Definitions of underrepresented populations beyond race and ethnicity

The MRCT Center appreciates that FDA has brought attention to inclusion of trial enrollment of other populations beyond race and ethnicity, such as sex, gender identity, socioeconomic status, age, disability, pregnancy and lactation status, and comorbidity. To that list, when appropriate, we would recommend the addition of geography (e.g., rural location), sexual orientation, educational attainment, nutritional status and food (in)security, and others. As noted by FDA, neither race nor ethnicity are causes in themselves of biological differences; social determinants of health, however, are important factors in health status and health outcomes. Further, intersectionality of race and ethnicity with other dimensions of diversity and with social determinants of health are meaningful and likely of scientific relevance. Only by collecting these data can their association on safety and efficacy be understood.

Similar to the comments above on the definitions of race and ethnicity, there are no standards for the collection of many of these other critically important variables. That is an initiative that we believe should be undertaken by FDA in collaboration with others. The regulated community needs data standards for data collection, both for standardization and for purposes of data aggregation and subsequent analyses.

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[2] See https://www.whitehouse.gov/wp-content/uploads/2017/11/Revisions-to-the-Standards-for-the-Classification-of-Federal-Data-on-Race-and-Ethnicity-October30-1997.pdf

Indeed, having common data standards will help with transposition of real-world data as well, to align subsequent interoperability and analyses.

D. Diversity in device regulations

One potential gap in the guidance are device studies for which an Investigational Device Exemption (IDE) is not required and for which, rather than pre-consultation with FDA, the sponsor obtains and relies on a 'Non-Significant Risk' or 'IDE exempt' determination from the IRB. The guidance does not appear to address these studies, which are common, or to make recommendations about when, or whether, to submit a Race and Ethnicity Diversity Plan to FDA for them (or whether, e.g., diversity plans should instead be submitted to the IRB, given that in these cases the IRB acts in the stead of the Agency in assessing the risk level of devices). It is also not clear whether or how this guidance is meant to apply to other types of studies where pre-consultation with FDA may not be the norm, such as bioequivalence/bioavailability (BE/BA) studies or trials that evaluate currently approved drugs for new indications and that may be Investigational New Drug (IND) exempt under 21 CFR 312.2(b).

E. Dynamic learning and improvement

The draft guidance formalizes the process and content of a Race and Ethnicity Diversity Plan, and while the concept of a plan submitted to FDA is not new,[3] this guidance will likely increase attention to the expectation. Sponsors are encouraged to describe "the successes and challenges in implementing [the Plan]" (line 165). Further FDA states that it "will evaluate the Race and Ethnicity Diversity Plan as an important part of the sponsor's development program" (lines 140-141). These plans will vary (1) in approach, detail, and specificity (e.g., degree of community engagement, recruiting strategies, etc.); (2) by condition and therapeutic area; (3) by study design and study design features, and (4) outcomes. In addition, the plans, recruitment, and outcomes will vary (5) by the geophysical location of the sites selected and the varying demographics of the populations they serve, and (6) by the demographics of the investigators and their study teams. FDA might consider whether collecting these additional data elements will enhance understanding. Taken together, each of these variables may contribute to the self-reported assessment of successes and challenges. The plans, assessments, and FDA evaluations will comprise an important source of information about how diverse recruitment can be accomplished successfully, efficiently, and respectfully. The MRCT Center encourages FDA to communicate or publish best practices and learnings periodically, after company confidential information is removed and sponsor identity are deidentified.

F. Public education

The MRCT Center recommends that FDA, in collaboration with other agencies and offices, endeavor to promote a public educational campaign to illuminate the benefits of collection of race and ethnicity data, as well as other variables of diversity, so that individuals appreciate why these data are important and to what purpose they will be used.

G. Participant protections

Protections against discrimination should be in place to protect the identity, societal benefits, and entitlements of participants who share their personal data. Avenues for recourse in the event of personal

[3] See: https://www.fda.gov/media/75453/download (page 3)

harm[4] should be available.[5] Moreover, it should be recognized that in recent months several U.S. states have adopted comprehensive privacy legislation that treats race and ethnicity as a sensitive category of personal information that is subject to heightened protection. This heightened protection includes in some cases affording individuals the right to opt-out of the processing of sensitive information or requiring that individuals affirmatively opt-in to the processing of such information prior to the collection of the information.[6] While some of these state laws contain exceptions for clinical research that may make these requirements inapplicable to information collected in a clinical trial, the scope of exemptions is not uniform and also may not apply to data collected in an RWD setting. FDA could highlight the continued evolution of state privacy laws and the necessity of taking such laws into account when designing strategies for collection of information concerning race and ethnicity and drafting clinical trial informed consent forms. Outside of the U.S., key privacy laws such as the European Union's General Data Protection Regulation also treat race and ethnicity data as subject to heightened protection, something with which sponsors of MRCTs must contend when seeking to collect data on racial and ethnic origin.

Thank you again for the opportunity to comment on this important issue. We believe that FDA has taken an important step in recommending that sponsors include a Race and Ethnicity Diversity Plan in advance of initiating applicable pivotal trials. The guidance, and specificity of the recommendations, are an important advance in calling attention to the inclusion of underrepresented populations in clinical research that informs medicines development and approval.

We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact the MRCT Center at bbierer@bwh.harvard.edu, sawhite@bwh.harvard.edu, mark.barnes@ropesgray.com, and david.peloquin@ropesgray.com.

Respectfully submitted,

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[4] For example, participant status as an undocumented immigrant.

[5] We note that FDA may not have authority to provide recourse in the event of personal harm, and that FDA may wish to or need to work with other government agencies to provide appropriate protections.

[6] *See, e.g.*, California Privacy Rights Act of 2020, effective January 1, 2023 (treating race and ethnicity as a sensitive category of information and providing data subjects the right to opt-out of the use and disclosure of such information); Colorado Privacy Act, effective July 1, 2023 (treating personal data revealing racial or ethnic origin as a sensitive category of information and providing that such data may only be processed if the individual provides opt-in consent to such processing); Connecticut Data Privacy Act, effective July 1, 2023 (treating personal data revealing racial or ethnic origin as a sensitive category of information and providing that such data may only be processed if the individual provides opt-in consent to such processing); Utah Consumer Privacy Act, effective December, 31, 2023 (treating personal data revealing racial or ethnic origin as a sensitive category of information and requiring that the individual be given the opportunity to opt out of the processing of such information); Virginia Consumer Data Protection Act, effective January 1, 2023 (treating personal data revealing racial or ethnic origin as a sensitive category of information and providing that such data may only be processed if individuals provide opt-in consent to such processing).