ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

June 13, 2022

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration, Dockets Management Staff
5630 Fishers Ln, Rm. 1061
Rockville, MD 20852

RE: ACRO comment regarding draft guidance entitled, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* [Docket No. FDA-2021-D-0789]

Dear Ms. Roth,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices, from pre-clinical, proof of concept, and first-in-man studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficacy, and safety of biomedical research.

ACRO thanks the Agency for releasing this draft guidance on *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*. ACRO is pleased to provide the following comments.

I. General Comments

ACRO is pleased to see the Agency developing guidance aimed at improving diversity and inclusion in clinical trials. ACRO and its members are strongly committed to this work and look forward to continuing to work with the Agency in this effort. With regard to this particular draft guidance, there are five areas on which we would like to focus our general comments.

Awareness. A significant barrier to participation in clinical trials by underrepresented populations in the lack of awareness of available trials or opportunities for healthy participants by community and primary care physicians. Health care professionals should be made aware of national, regional, or local trials currently recruiting patients as well as the eligibility criteria for each of those trials to discuss enrollment with their patients. Stakeholders should explain to communities and potential study participants the study question as it pertains to the diverse population target and what the study question could answer for the sub-group analysis. This could increase public confidence in both scientific integrity and ethics. Enhanced promotion of clinicaltrials.gov directed toward healthcare providers and potential study participants of all races and ethnicities could improve the inclusion of more diverse populations.

Leverage Data. The guidance should describe strategies to leverage patient and health care provider demographic data (disease prevalence, zip codes, prescriber data, etc.) to improve trial placement and increase the availability of clinical trials as a care option to all communities.

Accessibility. The guidance should include a discussion regarding clinical trial access and the intrinsic and extrinsic dimensions of diversity that impact participation including technology, logistics, relationships, and education. Possible burdens to participation should be explored including clinical trial appointment scheduling and logistics that will increase accessibility of clinical trial visits outside of typical office/business hours, such as expanded weekend/evening/early morning appointments, the use of virtual trial visits, and home health nurse visits where appropriate to further reduce the burden for patients, families, and investigative sites.

Enablement. Industry prioritizes prior research experience and documented performance as a key selection criterion for investigative sites making it exceedingly difficult for new physicians and sites to break into clinical research and offer the benefit of clinical trials as a care option to their patients. Some clinical research organizations (CROs) have developed comprehensive training and support programs for trial-naïve sites to broaden patient access to clinical trials and enhance the diversity of patient populations; however, sponsors are often reticent to utilize inexperienced research sites despite higher touch training and monitoring plans. To reach underrepresented patient populations with clinical trials, we need to bring trials to more physicians in a variety of settings. We recommend the guidance encourage industry to support the training of new research sites and site staff as well as include a higher percentage of these sites in each of their studies, where appropriate to do so.

Patient Insights. Increasing representation of diverse patient groups in clinical trials continues to be an evolving priority with many life science organizations. Previous FDA guidances such as *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) are a valuable resource for drug development stakeholders. However, as collective experiences have been limited, formalized guidance and recommendations are not only needed but will substantiate best practices with engaging broader and more diverse patient groups. Sponsors and their vendors should prioritize capturing patient insights and experience as a pivotal component of drug and device development for our biopharma and biotechnology customers. We understand the significance of integrating the patient voice into the clinical research continuum, which is why we respect and support the urgency to capture a more accurate and representative cross-section of patients.

II. Line-Specific Comments

Line Number	Current Text	ACRO Feedback
16-65	Introduction	For better context surrounding this issue, we recommend the Agency

		include a more detailed discussion on the complex issues that cause underrepresentation of racial/ethnic minorities, women, and elderly patients in clinical trials as described in detail in the 2014 FDA Report: FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data. Many historical and current barriers to participation have been described in detail: limited numbers of investigators who can help enroll underrepresented subgroups or who have access to a broader range of patient subgroups; patients and families with negative attitudes about medical research and concerns about risk, patient inconvenience, availability of transportation, geographic locations, and insurance status. In addition, both biological and social determinants of health must be included as considerations.
21-28	"Individuals from these populations are frequently underrepresented in biomedical research despite having a disproportionate disease burden for certain diseases relative to their proportional representation in the general population. Adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved, and may potentially identify effects on safety or efficacy outcomes that may be associated with, or occur more frequently within these populations."	It would be beneficial if FDA would define "highly relevant" populations. For example, would incidence in a particular race category need to be different from the incidence among the White subgroup by a statistically significant amount? Or would a race subgroup need to be significantly different relative to incidence rate for US population in general (all races)? What should serve as a baseline? What should each race subgroup be compared against? Would it be acceptable to set enrollment goals only for those race subgroups which have been determined to be "highly relevant."
33-39	"However, FDA advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented	It would be helpful if FDA could clarify expectations with regards to underrepresented populations. The recommended elements of a Diversity Plan makes reference to race and

	populations defined by demographics such as sex, gender identity4, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity. FDA encourages sponsors to also submit plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations."	ethnicity only. We need additional guidance on how to both set targets (data to consider) as well as to define diversity in context – sex, ability/disability, co-morbidities, etc. Recommendation for range +/- the target enrollment that would be acceptable, how is data reported as a rate (xx in 100,000 in US population) to be converted into meaningful percentages for use in setting enrollment goals? (Ultimately yielding enrollment goals of xx% of the clinical trial population that should be Black, xx% of the trial population that should be Asian, etc.)
41-44	"This guidance expands on FDA's guidance, *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016), which outlines how to collect and present race and ethnicity data in submissions to the FDA and recommends that sponsors develop and submit a plan to address inclusion of clinically relevant populations, for discussion to the Agency."	FDA's guidance, *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016), provides five specific race choices. There is currently no federal or social definition of race. In addition, FDA's guidance does not give an option for other races or for the categorization of biracial subjects. Further, the "Asian" category is broad and may not truly account for differences in drug metabolism and adverse drug reactions.
47-51	"…FDA recommends that a Plan to enroll representative numbers of participants from historically underrepresented racial and ethnic populations…"	It would be beneficial for FDA to define what it considers "representative," whether it is a particular percentage for the race and ethnicity based on predominance in the disease state and outline how this applies to small patient populations. ACRO suggests the inserting the below on line 51 immediately following the sentence that begins on line 47 with, "As described in further detail…": "A Plan is considered 'representative' if clinical trial participant demographics reflect the demographics of the disease prevalence, and, where the demographic of the disease is equal across race/ethnic groups, clinical trial participant demographics represent the country population demographics (e.g., in the US, use US Census data to

		determine the target race/ethnic group to be represented in each clinical trial)."
51-54	"This plan should be discussed with the FDA as soon as practicable during medical product development. For drugs, this should occur no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often during the End of Phase 2 (EOP2) meeting)."	It would be helpful if FDA could define which group within FDA sponsors need to work with to discuss Diversity Plans and whether there will be a specific group within each division or across divisions focused on providing feedback for Diversity Plans. We also request clarity on timelines for sponsors to provide Diversity Plans as early as the pre-IND meeting or no later than the EOP2 meeting.
93-97	"…evidence regarding safety and effectiveness across the entire population. Such measures could include but are not limited to offering financial reimbursement for expenses incurred by participation in a clinical trial or study (e.g., travel or lodging) providing language access to participants with limited English language proficiency, and partnering with community-based organizations to provide support to study or trial participants."	ACRO recommends that the guidance text include clarification that participants may be compensated commensurate to their working time missed to participate in the trial if approved by an IRB/EC approval in accordance with current regulations. We recommend that FDA encourage sponsors to work with IRBs to establish appropriate compensation.
132-141	"FDA recommends a Plan be submitted for medical products for which an IND submission is required and/or for which clinical studies are intended to support a marketing submission…"	The guidance should clarify whether there will be an option for sponsors to request a waiver or deferral (e.g., in instances such as rare disease or diseases that are population specific) and if so, FDA should describe the process for waiver or deferral consideration.
147-148	"Sponsors may discuss their strategy to enroll a diverse study population at any time throughout the medical product's development"	It would be beneficial if the FDA would clarify whether sponsors can request a meeting outside of a milestone meeting.
171-172	"Sponsors should define enrollment goals for underrepresented racial and ethnic participants as early as practicable in clinical development for a given indication."	Considering that most products are developed for a global market it would be useful if the FDA would address the acceptability of using foreign data to potentially represent some of the underrepresented populations or if the data must come from U.S. populations. Additionally, FDA should clarify if the satisfaction of enrollment goals reflecting US population/disease population can or should be achieved

		with only US sites, or if this will be a point of discussion for sponsors.
202-203	"When there are no data that indicate that race or ethnicity will impact safety or effectiveness, it is nonetheless appropriate that enrollment reflects the epidemiology of the disease."	The guidance should make clear if a Diversity Plan can then justify not needing to set quantitative, measurable enrollment goals.
215-218	"FDA encourages sponsors to leverage various data sources (e.g., published literature and real-world data) to set enrollment goals; if this is not feasible, it may be appropriate to set the enrollment goal based on demographics in the overall population with the disease or condition."	It would be helpful if the FDA could include examples of or references to the types of real-world data sources that can be leveraged to set enrollment goals and describe disease outcomes and demographics. Real-world data is not always complete, especially for race and ethnicity. It will be important for the FDA to advocate for completeness of real-world datasets.
219-220	"The Plan should include the clinical pediatric studies that are planned for inclusion as part of the pediatric development of the medical product."	The timing of the Race and Ethnicity Diversity Plan (Plan) will conflict with the timing of agreed upon Pediatric Study Plan (PSP). The FDA should provide clarity on whether its expectation is that the PSP be submitted sooner or that the pediatric studies presented in the Plan will be based on what the sponsor will propose in the initial PSP. In addition, the FDA should elaborate on their expectations regarding the expected representative pediatric patient population. ACRO suggests the following: "The Plan should include the proposed clinical pediatric studies that are planned for inclusion as part of the pediatric development of the medical product. Sponsors may update the Pediatric Diversity Plan after reaching an agreed upon Pediatric Study Plan."
225	Category 2	ACRO requests that the FDA clarifies the scope of this section—is "medical product development program" meant to encompass combination products?
225	Category 4B(ii) and 4B(iii)	ACRO suggests the following: "ii. Sustained community engagement (e.g., community advisory boards and navigators, community health workers,

		patient advocacy groups, local/community healthcare providers, etc.); iii. Reducing burdens due to trial/study design/conduct (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, in-home care, digital endpoints, decentralized clinical trial elements, telehealth)."
225	Category 5	Once the Plan is developed a sponsor should not change the Plan unless FDA directs it; rather, updates on the progress should be provided along with plans to address deficiencies if the goals fell short via the post-marketing studies. It would also be helpful to understand how progress should be communicated to FDA.

Thank you for this opportunity to provide feedback on the draft guidance. Please do not hesitate to contact ACRO (smcleod@acrohealth.org) if we can provide additional details or answer any questions.

Respectfully,

Sophia McLeod
Director, Government Relations