ACRO Innovate Advocate Collaborate

September 26, 2024

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

RE: Association of Clinical Research Organizations Comment Submission:
Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies
[Docket No. FDA-2021-D-0789-0111]

The Association of Clinical Research Organizations (ACRO) appreciates the opportunity to provide comments to the Food and Drug Administration's (FDA or Agency) recently updated draft guidance, *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*.

ACRO is made up of the world's leading clinical research and technology organizations. Our member companies are involved in the majority of industry-sponsored, FDA-regulated clinical trials in the United States and around the world. ACRO members provide an array of specialized services across the entire spectrum of drug, biologic, and medical device development—from discovery, pre-clinical, proof of concept, and first-in-human studies, through post-approval and pharmacovigilance research.

ACRO thanks the Agency for releasing this updated draft guidance. Please find our general and line-specific comments below.

General Comments

ACRO is pleased to see the Agency continuing its commitment to improving the representativeness of clinical trials by updating this draft guidance as directed by the Food and Drug Omnibus Reform Act (FDORA) of 2022. ACRO and its members are likewise committed to this work and look forward to continuing to work with the Agency in this effort.

We'd like to highlight a number of considerations for the Agency as work begins on a final guidance:

Diversity Enrollment Strategies: We commend the Agency for strongly recommending that sponsors develop and implement a comprehensive diversity strategy across the entire clinical development program, including in early phase studies. This will be extremely impactful as, for example, it will be challenging to understand potential pharmacokinetic (PK)/pharmacodynamic (PD) differences if early trials do not have representative enrollment across age, sex, race, or ethnicity. Stronger emphasis on the need to implement a diversity strategy in early phase trials is suggested, particularly for diseases and conditions that disproportionately affect underrepresented patient populations. The guidance should outline

how the Agency plans to address the inclusion of other underrepresented populations that are not defined by race, ethnicity, sex, or age, such as pregnant and lactating individuals, menopausal individuals, multi-racial individuals, and individuals with disabilities. The guidance requirements on rare disease product development, with limited knowledge of differential disease impact, has a potential impact. We would encourage the Agency to provide clarity on what flexibility will be provided for enrollment goals in these clinical trials.

The April 2022 draft version of the DAP guidance referenced the use of real-world data and literature searches to inform the enrollment goals. However, there is no mention of how real-world data could be used towards the enrollment goals in this updated version of the draft DAP guidance. We would ask the FDA to include the real-world data language from the 2022 DAP draft guidance in the upcoming final guidance. A persistent gap exists with real-world data whereby race and ethnicity data is often missing, and therefore emphasis on additional qualitative data from patient and community groups is useful. We recommend FDA, along with other Federal agencies, continue to pursue efforts to improve the completeness on race and ethnicity data or even sex/gender analysis on early phase data, and social determinants of health data for real-world data as it could be used to supplement clinical trial data over time across various demographics, even if it is not used to directly inform the enrollment goals.

Section C of the guidance recommends sponsors focus on community engagement to reach diverse populations. We support and commend this focus. We also note that the persistent barrier for what is needed for authentic community engagement—consistency—is challenging due to the episodic nature of clinical trials. Many sponsors have large, national initiatives to support communities and patient groups, but true engagement is local. In the clinical trial ecosystem, it is the sites who are in the position to stay connected with the community and trusted leaders, yet industry funding of site efforts via specific clinical trials leads to inconsistent engagement. We suggest the FDA convene sponsors, CROs, clinical technology vendors, sites, patient and community groups, and institutional review boards (IRBs) to explore both the practical realities and ethical challenges of funding consistent community engagement with the goal of developing models to support sites and community partners in more effective and beneficial community engagement. The FDA should be sure to include representatives from the range of sites supporting clinical research, both public (academic) and privately owned sites, in these discussions.

To facilitate assessment of legal requirements/restrictions in some jurisdictions, the guidance should include a definition of race and ethnicity/ethnic origin (not present in the January 2024 draft *Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products* either).

Global Studies: While the guidance states that multi-national studies should have a DAP for the entire study and acknowledges the lack of uniformity with data collection in the global setting, the guidance is unclear or does not contemplate the challenge of reflecting US population across a global study, given that many regions have homogenous populations that will skew the ability to reflect US demographics if the calculating of goals is done on the

entire global sample. Further discussion and contemplation of different scenarios is needed to balance the critical objectives of adequate representation to achieve generalizability to the US population yet in the context of a global trial

The Agency should also clarify whether data from different regions will be aggregated or kept separate with regard to patient diversity.

Accountability: The guidance does not outline potential enforcement measures for sponsors if DAP enrollment goals are not met or if certain expected actions are not taken, nor does it address the potential to impact FDA approval decisions and/or requirements for post-marketing requirements and commitments if DAP enrollment goals are not achieved. ACRO recommends the FDA focuses on accountability rather than consequences and should align with the intent of the guidance, which is to increase enrollment of underrepresented populations clinical trials. We suggest the FDA consider thresholds of compliance, that includes measures that may not be outcome-based like other compliance standards in the industry.

Sample compliance measures could include:

- Documentation of the existence of certain actions within certain timeframes.
- Minimums or maximums of certain efforts.

Going forward we suggest that the Agency articulate options that could set expectations around meaningful measurement and evaluation with clear expectations where non-compliance or threshold impacts are not being reached during interim transparency reporting or once trials have completed.

DAP Availability: The guidance encourages public posting of DAP information on sponsors' websites. To enhance public visibility and transparency, the FDA should share when such information is or is not posted by the sponsor and provide a link to that information on the Drug Trial Snapshots page, or other FDA sponsored public location.

Format: We welcome additional clarity on the structure and content for the annual reports filed by IND application holders.

Line-Specific Comments

Line Number	Current Text	Concern	ACRO Feedback
111-114	Factors to consider when setting enrollment goals include demographic characteristics (e.g., race, ethnicity, sex, age group), clinical characteristics (e.g., presence of	The current text is not aligned on the factors that are primarily mandated to guide setting enrollment goals as per sections 505(z) and 520(g)(9) of the FD&C Act and FDORA	Primary and mandatory factors to consider when setting enrollment goals, as per FDORA, include demographic characteristics (e.g., race, ethnicity, sex, age group). Additional factors

	comorbidities, disease etiology), and other characteristics (e.g., access to standard preventive and diagnostic care, access to standard treatments of the clinically relevant population).	that, respectively, require sponsors to submit a Diversity Action Plan that specifies goals for clinical study enrollment, and that such goals must be disaggregated by the race, ethnicity, sex, and age group demographic characteristics of the clinically relevant population—as described in lines 187-190.	to consider in assessing population diversity include clinical characteristics (e.g., presence of comorbidities, disease etiology), and other characteristics (e.g., access to standard preventive and diagnostic care, access to standard treatments of the clinically relevant population).
243-251	In such cases, the sponsor's enrollment goals specified in the Diversity Action Plan for each study should consider how individual clinical studies fit into an overall clinical development program for the medical product (i.e., for a particular indication or intended use), and how such individual studies should help generate data representing the clinically relevant population's demographic characteristics consistent with the incidence or prevalence in the disease population for the program. In such a situation, the Diversity Action Plan for each clinical study should reflect a strategy that leads to an overall proportionate representation, even though individual clinical studies may not have proportionate representation.	This text should be simplified considering this is a straightforward message that sponsors conducting multiple Phase III or pivotal trials don't necessarily need proportional representation in every individual study, but in the totality of pivotal studies.	In such cases, the sponsor's enrollment goals specified in the Diversity Action Plan for each study does not need proportional representation in every individual study but should reflect a strategy that leads to an overall population representative of the demographic characteristics of the intended treatment population.

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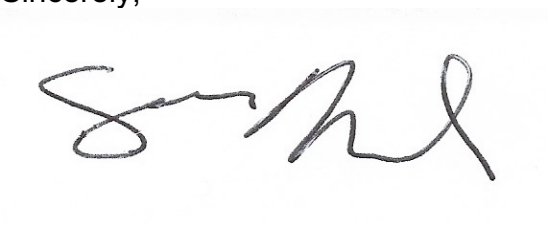
Conclusion

Thank you again for the opportunity to comment on this important draft guidance. Ensuring that the clinical trials we run are truly representative of the patients with the condition we are aiming to treat is paramount to the future of drug development.

Please do not hesitate to contact ACRO if we can provide further details or answer any questions.

Sincerely,



Sophia McLeod
Sr. Director, Government Relations
smcleod@acrohealth.org