Alliance for Regenerative Medicine

September 26, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20857

Re: FDA-2021-D-0789; *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies; Draft Guidance for Industry*

To Whom it May Concern,

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to comment on the draft guidance document, *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies.*

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

ARM wholeheartedly supports FDA's goal of improving representation in clinical trials, particularly for populations historically underrepresented in medical research. ARM maintains its commitment to the breadth of responsibilities a sponsor must maintain to operate a clinical trial that aligns with the mission, vision, and shared values of the Agency. We also recognize the practical challenges that sponsors face in operationalizing efforts to achieve these goals. ARM respectfully requests the Agency consider certain recommendations to balance diversity objectives with the realities of clinical trial enrollment, particularly for rare diseases and novel therapies like cell and gene therapies.

General Comments

Rare Disease Populations and Novel Therapies

ARM acknowledges the inherent challenges of enrolling patients in rare disease trials.

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The difficulties of small patient populations are exacerbated by the limited availability of clinical sites for novel therapies, such as cell and gene therapies. For instance, due to their complexity, many of these therapies can only be administered in specialty clinics that are only available in select locations, further complicating recruitment, particularly for rural populations. We encourage the Agency to provide flexibility in these cases by allowing supplemental data collection on underrepresented populations to occur post-market (where needed), as suggested in the FDA's separate guidance on postmarketing data collection[1].

Race/Ethnicity Categories

The FDA's recommended race categories may not align with data available in certain registries or previously published studies, where broader categories (e.g., Asian/Pacific Islander) are often used. In these cases, we ask that the FDA allow for flexibility in combining race categories or setting enrollment goals based on available data sources when more granular demographic breakdowns are unavailable. Thoughtful consideration will be necessary to leverage global data where race and ethnicity categories are not aligned with those in the US or otherwise limited in sponsors ability to collect such data due to local privacy regulations.

Postmarketing Commitments and Requirements (PMCs/PMRs)

We request indication of factors that could trigger a postmarketing requirement (PMR) for failure to meet DAP enrollment goals. We believe that postmarketing mechanisms should only be mandated when significant gaps in enrollment occur, which could lead to risks not being fully identified during premarket clinical trials. Without strong rationale to gather additional safety or efficacy data, FDA should use postmarket mechanisms sparingly as they place a significant burden on sponsors and patient communities.

Transparency and Public Sharing of DAP Information

While we recognize the importance of transparency to build trust within underrepresented communities, we ask the FDA to clarify its expectations for sharing DAP information with the public. Specifically, we recommend that these efforts not be included as a formal DAP submission but instead discussed with the Agency during sponsor meetings to ensure alignment with FDA's intent.

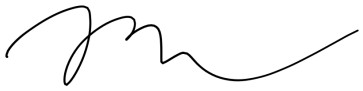
Intersectionality and Additional Demographics

We note FDA's encouragement to sponsors to consider additional demographic factors including, but not limited to geographic location, gender identity, sexual orientation, and socioeconomic status (SES), as well as English-language proficiency. ARM appreciates the Agency's attention to intersectionality and recognition of the broader issues of health disparities and differential access to health care and clinical studies which may occur due to those additional factors.

[1] Postmarketing Approaches To Obtain Data on Under-Represented Populations in Clinical Trials; Draft Guidance for Industry; [Docket No. FDA-2022-D-2629]; https://www.fda.gov/media/170899/download

In conclusion, we fully support the FDA's efforts to enhance diversity in clinical trials to optimize their ability to accurately characterize real-world performance and believe that flexibility is essential to address specific challenges, especially in rare disease and global studies. We look forward to continuing our collaboration with the Agency to ensure that these goals are met without hindering the timely completion of critical clinical trials. Please see specific line-by-line comments below relating to the above themes.

Sincerely,
Monica Veldman



Director, Global Regulatory Policy
The Alliance for Regenerative Medicine (ARM)

Specific Comments

II. BACKGROUND		
Lines/Section /Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
112	"...clinical characteristics (e.g., presence of comorbidities, disease etiology)..."	The disease etiology can be unclear, complex and multifactorial. We recommend adding the following red underlined text to clarify: Factors to consider when setting enrollment goals include demographic characteristics (e.g., race, ethnicity, sex, age group), clinical characteristics (e.g., presence of comorbidities, well established disease etiology), and other characteristics (e.g., access to standard preventive and diagnostic care, access to standard treatments of the clinically relevant population).
178-181	"While sponsors are required to submit a Diversity Action Plan for the studies specified above, FDA	We seek clarity on whether the clinical development program refers to late stage and early stage, e.g. relapsed/refractory and newly

	strongly recommends that sponsors develop and implement a comprehensive diversity strategy across the entire clinical development program, including in early studies, when possible."	diagnosed oncology setting. ARM suggests being able to combine multiple development programs (e.g. sub-q & IV), where justified into a single DAP submission, see additional proposed red underlined text: While sponsors are required to submit a Diversity Action Plan for the studies specified above, FDA strongly recommends that sponsors develop and implement a comprehensive diversity strategy across the entire clinical development program, including in early studies, when possible. Where justified, sponsors may combine data across similar clinically relevant patient populations (e.g. second combined third line setting, sub-q combined with IV formulation) to inform a holistic, single Diversity Action Plan submission.

IV. ADDRESSING RACE, ETHNICITY, SEX, AND AGE GROUP IN DIVERSITY ACTION PLANS		
Lines/Section /Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
193-198	"Sponsors should consider whether certain demographic groups (e.g., older patients, pediatric patients, females, a particular race or ethnic group or combinations thereof) may have a different response to the medical product—either differential effectiveness or safety (e.g., based upon differential pharmacokinetics (PK), pharmacodynamics (PD), or due to possible differences in susceptibility to specific adverse events of concern for a drug or medical device), or due to differential presentation of the disease or condition."	Data may not be available regarding the response to a specific medical product by demographic groups, especially for those in the early phase of development. We request the addition of the following red underlined text to add flexibility: Sponsors should consider whether certain demographic groups (e.g., older patients, pediatric patients, females, a particular race or ethnic group or combinations thereof) may have a different response to the medical product—either differential effectiveness or safety (e.g., based upon differential pharmacokinetics (PK), pharmacodynamics (PD), or due to possible differences in susceptibility to specific

		adverse events of concern for a drug or medical device), or due to differential presentation of the disease or condition (if applicable).

V. CONTENT OF THE DIVERSITY ACTION PLAN		
Lines/Section /Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
A. Enrollment Goals		
262-264	"When using non-publicly available sources (e.g., electronic health records, certain registries, or other privately held information sources) to derive incidence/prevalence estimates…"	We recommend adding claims data as an available source to obtain information: When using non-publicly available sources (e.g., electronic health records, claims data, certain registries, or other privately held information sources) to derive incidence/prevalence estimates…
288-294	• "For a clinical study designed to investigate a medical product that is intended for a general use population (e.g., preventive vaccine), it may be acceptable to set enrollment goals based on general U.S. population demographics (i.e., U.S. census data). • For a clinical study designed to investigate a medical product in a population for which there are limited or no data or information to characterize the demographic characteristics of the intended use population, it may be acceptable to set	If the intended subpopulation is not prevalent, recruitment may be untenable without allowing the global recruitment to capture all subpopulations. We recommend adding the term "global" within the text: For a clinical study designed to investigate a medical product that is intended for a general use population (e.g., preventive vaccine), it may be acceptable to set global enrollment goals based on general U.S. population demographics (i.e., U.S. census data). For a clinical study designed to investigate a medical product in a population for which there are limited or no data or information to characterize the demographic characteristics of the intended use population, it may be acceptable to set global enrollment goals based on general

	enrollment goals based on general U.S. population demographics (i.e., U.S. census data)."	U.S. population demographics (i.e., U.S. census data).
297-302	"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 multinational clinical study must describe participant enrollment goals for the entire study and should not be limited to U.S.-enrolled participants."	Per the draft guidance, 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. We request clarification on whether enrollment goals by demographic characteristics, and the estimated prevalence or incidence of the disease/condition by demographic characteristics in a non-US population should also be provided, or preferably, only composite global goals (which include US goals). We also request clarification for instances in which the estimated prevalence/incidence by demographic characteristics in other countries are unavailable or out of date. Presumably, sponsors would use US figures to set global goals in this instance.
300-305	"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."	We request clarification on whether the DAP is expected to outline the strategy to enroll this goal globally. "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. In practice, if U.S. prevalence suggests 20% of black/African American population, the sponsor is expected to outline the strategy to reach this 20%

		enrolment goal with patients globally (including site/country selection choices). "
305-311	"FDA recognizes that the lack of uniformity across the globe in the use of population descriptors such as race and ethnicity may pose challenges when setting enrollment goals for international sites. For example, it may be challenging to identify corresponding populations defined on the basis of race or ethnicity when describing the affected population outside the U.S. and consequently, when setting enrollment goals for the clinical study. Sponsors should consider FDA guidance when describing and presenting population race or ethnicity for the purposes of setting enrollment goals."	Per the draft guidance on the Collection of Race and Ethnicity Data in Clinical Trials and Clinical studies for FDA-Regulated Medical Products (January 2024)[2], regarding race - it is recommended to use categories American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. It can be challenging to inform enrollment goals for each of these race categories when registry data/previously published studies use different race categories (e.g., Asian/Pacific Islander, non-Hispanic Black, and non-Hispanic White). We suggest the Agency include their perspective on how to address this potential disconnect such as the ability to combine racial categories or use a different set of racial categories when appropriate, see added underlined text: FDA recognizes that the lack of uniformity across the globe in the use of population descriptors such as race and ethnicity may pose challenges when setting enrollment goals for international sites. For example, it may be challenging to identify corresponding populations defined on the basis of race or ethnicity when describing the affected population outside the U.S. and consequently, when setting enrollment goals for the clinical study. Sponsors should consider FDA guidance when describing and presenting population race or ethnicity for the purposes of setting enrollment goals. Where there is a lack of appropriately disaggregated global data sources, sponsors may set targets based on US data and

[2] Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for Food and Drug Administration-Regulated Medical Products; Draft Guidance for Industry; [Docket No. FDA-2016-D-3561]; https://www.fda.gov/media/175746/download.

		combine racial categories when justified by available literature/data sources.

VII. PROCEDURES FOR SUBMITTING THE DIVERSITY ACTION PLAN AND RECEIVING FEEDBACK		
Lines/Section /Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
489-492	"Depending on the specifics for each clinical development program, the relevant Division in CDER or CBER may or may not provide feedback on the Diversity Action Plan. FDA feedback on a new or revised Diversity Action Plan may be at FDA's initiative or per the sponsor's specific request for feedback."	We recommend the Agency set a timeframe (e.g., 90-day review period) for providing feedback for DAPs if the sponsor requests it, or if the FDA perceives deficiencies in the sponsor's DAP.