AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036-4929 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

September 26, 2024

Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Submitted electronically at www.regulations.gov

RE: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies - Draft Guidance (Docket No. FDA-2021-D-0789)

Dear Dr. Califf,

The American Society of Hematology (ASH) appreciates the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) in response to the draft guidance on *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (Docket No. FDA-2021-D-0789).

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease (SCD). In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

ASH has a longstanding commitment to combating inequities in healthcare and research; and in 2021, the Society released a Statement on Addressing Diversity, Equity, and Inclusion in Hematology Research, Practice, and Training. We commend the Agency for releasing this draft guidance, which details the requirements for a clinical trial sponsor's Diversity Action Plan (DAP). The implementation of a DAP has the potential to improve the participation of underrepresented populations in clinical trials. Our members believe that this guidance will encourage sponsors to incorporate critically diverse participation in their trials since they will be held accountable to demonstrate diversity in trial recruitment. This is particularly important given the need for clinical trial populations to reflect the demographics of the populations that will ultimately use the medical products.

In hematology, for example, certain populations have historically been both underrepresented and disproportionately affected by diseases such as lymphoma and multiple myeloma. In multiple myeloma, the elderly and Black individuals are often not adequately represented in trials despite the disease heavily impacting those populations. (1) While significant improvements have been made, survival outcomes for women, the elderly, and underrepresented racial/ethnic groups remain consistently lower than for men and non-Hispanic whites. (2, 3, 4, 5) To address this, the Society has developed the ASH Diversity, Equity, and Inclusion (DEI) Toolkit for Clinical Trial Sponsors, to help investigators weave DEI principles throughout the clinical trial lifecycle (from formulation of the research question

through to the dissemination of results). ASH believes this is a practical and valuable resource that will help hematology investigators align with the DAP recommendations. Additionally, the Society encourages the FDA to promote compliance with the DAP by highlighting practical tools such as the ASH Toolkit along with other resources (e.g., the DRIVE initiative (6, 7)) aimed at increasing trial participation from underrepresented individuals.

ASH believes this guidance is a positive step toward improving the representation of underrepresented populations in clinical trials. However, to create a lasting impact, a strong commitment from investigators is essential. The Society commends the Agency for specifically noting key components to address known challenges, such as leveraging community-based sites. Further, ASH encourages the FDA to clarify in the guidance what sponsors would need to do if their enrollment goals are not achieved and to detail how the Agency will handle such cases. Making certain that investigators are held accountable for designing trials that are reflective of the epidemiology of the disease is a crucial step for the development of study results that are generalizable, and it is within this context that we offer the following comments:

Content of the DAP

The draft guidance outlines three required sections of a DAP, including (1) The sponsor's goals for enrollment in the clinical study, disaggregated by race, ethnicity, sex, and age group of clinically relevant study populations; (2) The sponsor's rationale for its enrollment goals; and (3)
An explanation of how the sponsor plans to meet its enrollment goals.

Enrollment Goals

ASH believes that enrollment goals disaggregated by race, ethnicity, sex, and age groups are appropriate for most hematology-related clinical trials, particularly phase III clinical trials. However, it is important to note that this may be difficult for certain diseases that are rare or specific to certain populations, like SCD and multiple myeloma which predominately impact Black people. As noted above, ASH encourages the FDA to clarify in the guidance what would happen if the enrollment goal is not achieved; and how the Agency would address circumstances when this goal is not met.

ASH appreciates that the guidance encourages sponsors to 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 medical products intended for the prevention, treatment, mitigation, cure, or diagnosis of hematologic diseases. We envision that it may be challenging to enroll both pediatric and adult patients in the same trial given potential different dosing. Therefore, we encourage the agency to recommend careful consideration and planning in its guidance to ensure that the trial design(s) can effectively address the unique needs of each demographic group while maintaining rigorous scientific standards.

It is also important to note that racial and ethnic identities are fluid and complex, and the FDA's categories may not fully capture participants' lived experiences. The focus on biological differences based on race has often overshadowed social and economic factors, which can contribute to disparities, perpetuating stigma and widening healthcare gaps. It is crucial to balance ethical data collection with the need for meaningful representation in trials. Therefore, ASH encourages the FDA to consider the importance of other forms of diversity, including sexual orientation, gender identity, physical abilities and disabilities, cultural background, and socioeconomic status.

Additionally, the draft guidance states that sponsors should select study sites and design studies to enroll populations representative of the U.S. intended use population, while accounting for challenges in using race and ethnicity descriptors at international sites and adhering to the FDA guidance when setting enrollment goals. When considering site selection in enrollment, it is important to note that there are centers whose patient populations do not reflect the diversity of the surrounding community. Allowing continued use of such centers may continue to exclude patients from underrepresented groups. Therefore, ASH recommends that the FDA

include stronger language on site selection to ensure diverse representation and access, especially for large phase III trials. Specifically, we recommend the following changes to lines 416-420 on page 17.

> *Improving access to the clinical study by limiting clinical study exclusion criteria,* ***and intentionally selecting*** *clinical study site locations that would facilitate enrollment of a representative study population (e.g., initiating the clinical study in sites that serve demographically diverse populations and that have prior experience enrolling diverse study participants in clinical studies), and considering the accessibility needs of persons with disabilities.*

ASH appreciates that the FDA recognizes the importance of global medical product development. The draft guidance states that a DAP for a multinational clinical study must describe participant enrollment goals for the entire study and should not be limited to U.S.-enrolled participants. It is important to note that currently many large phase III trials predominantly enroll participants outside the U.S. However, ASH believes the guidance is not well-suited for these international studies. One challenge is that each country where a global trial is conducted might have different parameters for the collection of demographic data. As such, sponsors of such trials could have challenges complying with the DAP. Additionally, the guidance groups certain races while failing to account for distinctions within these groups. For example, a Finnish individual may have more genetic differences from other White individuals than from people in other categorized groups.

To address these challenges, ASH encourages the FDA to work with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, to harmonize demographic data terminology and the collection of demographic data for global studies. This can help promote more accurate representation and enhance the relevance of trial results across diverse populations globally.

Requesting DAP Waivers

While our members recognize that a waiver could be necessary for rare disease trials that impact very small patient populations, many cited concerns with the inclusion of this provision in the DAP because it could discourage investigators of such trials from making attempts to engage diverse individuals in their studies. To that end, ASH encourages the FDA to give careful consideration to its guidance on the request for waivers and perhaps consult with experts in some of these rare disease areas prior to finalizing the guidance. Should the FDA deem it relevant to maintain this provision for a waiver, ASH suggests that the Agency request sponsors to include data to support why a diverse demographic can not be attained in the relevant disease area, and state why potential attempts to achieve diverse enrollment for this population will be futile.

Sponsor Public Posting of Key Information from DAPs

The FDA urges sponsors to publicly share strategies for meeting DAP enrollment goals. The draft guidance suggests posting key information online, including enrollment targets by race, ethnicity, sex, and age, along with steps taken to meet these goals. ASH believes that enhancing transparency will not only foster trust but also encourage broader participation in clinical studies. Additionally, this information can be utilized by patient advocacy and community engagement groups to support trial enrollment and diversification.

Publicly sharing DAPs will improve accountability and ensure that recruitment efforts are actively advancing diversity. Sharing successful strategies can help scale efforts and avoid common mistakes and this increased openness will further demonstrate a commitment to inclusive research practices. Transparency is essential, and sharing key information that promotes a diverse, real-world representation of individuals within a specific disease state should be encouraged. Publicly sharing enrollment goals and strategies should be done in a way that does not risk divulging critical, confidential information related to the clinical trial. As long as the shared information does not compromise the study's success, we believe it would be appropriate to disclose goals and strategies.

We appreciate the opportunity to provide these comments and look forward to any response you might have. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have

any questions or would like to arrange a meeting with the Society, please use ASH Director of Government Relations and Public Health, Stephanie Kaplan (skaplan@hematology.org or 202-776-0544), as your point of contact.

Sincerely,

Mohandas Narla, DSc
President

---

1. Habr D, Corsaro M. Reimagining diversity in multiple myeloma clinical trials. Hematol Oncol. 2022 Oct;40(4):689-694. doi: 10.1002/hon.2997. Epub 2022 Apr 13. PMID: 35391496; PMCID: PMC9790672.
2. Kuroki RS, Al Ali NH, Beg MS, et al. Outcome of diffuse large B-cell lymphoma in the United States has improved over time but racial disparities remain: review of SEER data. Clin Lymphoma Myeloma Leuk. 2011. ;11(3):257-260.
3. Evens AM, Antillon M, Ashbrook-Kilfoy B, Chiu BC. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. Ann Oncol. 2012. ;23(8):2128-2137.
4. Daniel Arthur Ermann et al., Racial disparities affecting Black patients with diffuse large B-cell lymphoma. JCO 40, 75077507(2022). DOI: 10.1200/JCO.2022.40.16_suppl.7507
5. Khullar K, Rivera-Nunez Z, Jhawar SR, et al. Pediatric Hodgkin lymphoma: disparities in survival by race. Leuk Lymphoma. 2020. ;61(3):546-556.
6. Maya N. Birhiray, Ruemu E. Birhiray; Practical strategies for creating diversity, equity, inclusion, and access in cancer clinical research: DRIVE. *Blood Adv* 2023; 7 (8): 1507–1512. doi: https://doi.org/10.1182/bloodadvances.2022008220
7. https://www.indyhematologyreview.com/drive/