



AMERICAN SOCIETY OF HEMATOLOGY

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June 10, 2022

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

Re: Draft Guidance for Industry — *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* (Docket No. FDA-2021-D-0789)

Dear Dr. Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) on the Agency's draft guidance on *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* (Docket No. FDA-2021-D-0789).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 non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. 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*](#). The statement underscores that *health inequities in medical research are evident through a lack of research on certain diseases for certain populations and a lack of diversity in clinical trials*. A lack of diversity in clinical trials also leads to health inequities in medical research and, ultimately, practice. Ensuring that clinical trials reflect the composition of a diverse society is important, allowing researchers and physicians to better understand how diseases impact different populations, why they tend to disproportionately impact some populations over others, and (especially in the age of precision medicine) how treatments can be tailored to individual patients or a subset of patients. The medical community has learned that a one-size-fits-all approach is not ideal, but in order to understand how to most effectively treat every patient, there must be diverse representation in clinical trials.

ASH continues to take steps to address these inequities, including the launch of the ASH Research Collaborative Sickle Cell Disease (SCD) Clinical Trials Network to enhance and accelerate the conduct of clinical trial research for SCD – a disease that illustrates critical health disparities and inequities. The Society is pleased to see the FDA's shared commitment to addressing inequities by increasing enrollment of diverse populations in medical product and drug development.

2022

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There are a number of hematologic conditions that would greatly benefit from increased diversity in related clinical trials. Multiple myeloma, for example, disproportionately affects African American or Black individuals—who are twice as likely to present with this disease compared to their white counterparts.ⁱ And even with the potential genetic advantages associated with a better prognosis, Black patients have lower survival rates. While African American or Black patients account for 20% of patients with multiple myeloma in the United States, in a review of multiple myeloma trials leading to FDA approvals between 2003 and 2017, the enrollment of these individuals was less than 5%.ⁱⁱ

ASH commends the FDA for releasing this important draft guidance with the goal to improve clinical trial diversity, and the Society supports the overall recommendations included in the document. ASH is pleased to share the following comments about where additional clarification in the guidance would be beneficial, and other important points for the FDA to consider that would help support the successful implementation.

GENERAL FEEDBACK

- **Sample Plan Needed** – The guidance addresses many important points in clinical research; however, we are concerned that the general, high-level statements throughout the document will be challenging for researchers to implement without more specific and focused examples. ASH recommends that the FDA include a detailed example “Plan” in the guidance to help guide sponsors toward creating actionable strategies. If a sample plan is not possible, ASH encourages FDA to provide technical assistance trainings on how to develop and implement a Race and Ethnicity Diversity Plan when the final guidance is released.
- **Potential Barriers to Implementation** – The provisions in the draft guidance, should they be implemented, are likely to have a positive impact on traditionally underrepresented races and ethnicities for the reasons articulated in the draft’s *Background* section; however, ASH shares the following concerns that could impact the success of the guidance:
 - ASH recommends that FDA more clearly articulate in the guidance how the Agency will hold sponsors accountable if they do not abide by the directives outlined. Sponsors may fail to take this action seriously if there is no clear directive from the FDA stating that lack of a diversity plan and/or diverse patient population in a clinical trial will impact the review of their study by the Agency.
 - The plan should allow for flexibility for the sponsors to ensure that patients predominantly impacted by the disease are represented in the study. While racial and ethnic diversity is important, it is also imperative that policies allow for investigators to recruit an adequate number of patients that are representative of the population predominantly impacted by the disease.
- **Harmonizing FDA Guidance on Diversity in Clinical Trials** – ASH encourages the FDA to ensure that this guidance and the Agency’s other policies do not inadvertently limit enrollment rates and lead to slower and/or decreased accrual and approvals overall. While this guidance is focused on racial and ethnic diversity, ASH recognizes that FDA has additional guidance on other important demographics in clinical trials, such as for sex-based disparities and older adults. The different guidances have varying degrees of details and directives that vary from this guidance. For example, the guidance on *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* is much more specific, directive, and expansive than this proposal. It includes responsibilities for each party (sponsor and investigator), specific tasks by stage of drug development, and recommendations on statistical design and analysis. We believe that having guidance documents that follow different structures for different demographics could lead to confusion in a sponsor’s development of a clinical trial protocol. ASH encourages the Agency to synchronize guidance across race, ethnicity, gender and age to avoid confusion and ensure successful implementation of all related guidance documents.

- ASH urges FDA to add language encouraging sponsors to work with healthcare providers to ensure that they are offering clinical trials to their patients. Research has shown that patients are more likely to participate in a trial if they hear about it from their trusted provider.ⁱⁱⁱ

GAPS and ADDITIONAL CLARIFICATION NEEDED

- **Introduction**

- The *Introduction* (Lines 51-54) and *Section IV(A)* (Lines 149-154) state that the Race and Diversity Plan should be discussed by sponsors with FDA no later than the end of phase 2 of the clinical trial. ASH encourages FDA to update the guidance to recommend that such discussion and plan development should occur as the trials are being designed and preferably prior to phase 1 studies being implemented. This is important because pharmacokinetics (PK)/pharmacodynamics (PD) that are meant to determine the safety and tolerability profile of a therapy should be studied in diverse patient populations before a therapy can be advanced to phase 2. Additionally, there are many hematology products that seek and are granted FDA approval based on a phase 2 trial. Suggesting that the Plan be discussed starting at the end of Phase 2 would not work for these types of trials as many earlier phase trials are used for approval or off-label expansion of indications.

- **Section V**

- Section V Lines 196-207 – The statements about enrollment reflecting epidemiology in this section are vague. ASH recommends that FDA add specificity about trials reflecting the epidemiology of the population afflicted by the disease within the United States.

- **Category 1 – *Overview of the disease/condition***

- ASH encourages the FDA to add a bullet to Category 1 that requires the sponsor to provide data showing the difference in populations predominantly impacted by the disease and people who are actually enrolled. This will ensure that sponsors are being more focused in their approach to enroll the patients that might benefit the most from the therapy. A valuable and recent example of this was Moderna's active strategy to stop recruitment of white patients in their COVID-19 vaccine study and focus more on recruiting black patients since that group was disproportionately impacted by the disease.

- **Category 4 - *Specific plan of action to enroll and retain diverse participants***

- Diverse enrollment teams will need more insight or suggested techniques to be successful in Category 4. ASH recommends that FDA add the following verbiage to address the gaps in this category: *Cultural tailoring, specific considerations to health literacy, examples of communication channels such as websites, social media and digital advertisements, etc.* We note that these items are addressed in the *Community Engagement* section, but we believe that the list should also be added to Category 4.
- The guidance implies that prespecified race/ethnicity metrics should be actively monitored during the course of trials, but the issue of active data monitoring is not made explicit. ASH recommends adding a bullet to Category 4 that clearly states that race/ethnicity metrics should be actively monitored, with a clear recommendation that this monitoring be part of the purview of the steering committee or Data and Safety Monitoring Board (DSMB) for the trial. The related reporting will help clinicians evaluate how applicable the therapy is for the patient that they are treating.

- ASH recommends adding a statement to this section that highlights how high-quality trial-related care and retention after enrollment is essential for positive patient experiences and may also reduce mistrust and improve future enrollment diversity.

ASH appreciates the opportunity to provide these comments. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (skaplan@hematology.org or 202-776-0544) as your point of contact.

Sincerely,



Jane N. Winter, MD
ASH President

ⁱ Bassel N, et al. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. *Am Soc Clin Oncol Educ*. 2019 May 17;39:3-10. doi: 10.1200/EDBK_100021.

ⁱⁱ FDA-AACR workshop to examine under-representation of African Americans in multiple myeloma clinical trials. U.S. Food & Drug Administration. <https://www.fda.gov/drugs/fda-aacr-workshop-examine-under-representation-african-americans-multiple-myeloma-clinical-trials>. Published February 13, 2020.

ⁱⁱⁱ [The Need for Awareness of Clinical Research | National Institutes of Health \(NIH\)](#)