September 25, 2024

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
Docket No. FDA–2019–N–5959
5360 Fishers Lane
Room 1061
Rockville, MD 20852

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Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies; Draft Guidance for Industry

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies: Draft Guidance for Industry. ACS CAN advocates for evidence-based public policies to reduce the cancer burden for everyone. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. By engaging advocates across the country to make their voices heard, ACS CAN influences legislative and regulatory solutions that will end cancer as we know it, for everyone. We are providing comments on the proposed rule through the lens of cancer patients.

ACS CAN commends the U.S. Food and Drug Administration (FDA) for recognizing the importance of enrolling representative numbers of participants from all racial and ethnic populations in the U.S. in clinical trials. The proposed Guidance describes the format and content of Diversity Action Plans (DAPs) which specify the sponsor's enrollment goals for a study, the rationale for those goals, and the mechanisms for meeting those goals. Improving clinical trial diversity is an important step toward realizing the aims of President Biden's Cancer Moonshot to reduce the cancer death rate by at least 50 percent over the next 25 years and improve the experience of living with and surviving cancer. Our comments seek to represent the perspective of cancer patients and therefore include considerations that differ slightly from those for clinical trials in other disease areas.

Background

Compared to their cancer burden, some racial and ethnic populations in the U.S. are vastly underrepresented in cancer clinical trials that support new drug approvals. Narrow clinical trial eligibility criteria have been shown to disproportionally affect population subgroups: Black patients (24%) and racial subgroups classified

as "other" (23%) had higher ineligibility rates than White patients (17%).[1] Another recent study of precision medicine trials encompassing 5,867 enrollees with race and ethnicity data calculated observed-to-expected ratios for population subgroups found that White participants were overrepresented in all studies, while Black, Hispanic, and American Indian and Alaskan Native participants were underrepresented.[2]

A key driver of the lack of representation of certain U.S. racial and ethnic populations in cancer trials is that industry-sponsored cancer trials heavily recruit participants from international sites. For example, FDA's annual Drug Trials Snapshot Report for 2023 showed that among the 4,504 patients that participated in trials that led to the approvals of 14 new oncology drugs, only 22.5% were from sites in the U.S.[3] From 2008 to 2018, the overall proportion of Black patients was less than 3% in global, pivotal trials supporting new U.S. FDA cancer drug approvals.[4] Notably, during this time Black individuals represented 12.1% of the U.S. population with cancer.[4] A similar study found that compared with White participants, Hispanic participants were underrepresented relative to their proportion (44% of expected proportion) of the U.S. cancer population in globally recruiting trials leading to FDA drug approvals over the same ten-year period.[5]

Racially and ethnically diverse clinical trials advance both ethical and scientific goals of research. Diversity in trials contributes to the ethical principle of justice by ensuring that no single group receives a disproportionate benefit or bears a disproportionate burden of clinical research. This principle serves as a key tenet of the biomedical ethics framework in the U.S, outlined in the *Belmont Report*.[6] The scientific goals are to create confidence that the results observed in the clinical trial will be applicable to the larger population with a disease or condition and, in some cases, the ability to understand subgroup differences in outcomes or safety. Diverse trial participants that are reflective of the broader disease population can help achieve these goals. Underrepresentation of racial and ethnic populations within the U.S. in trials could lead to the use of new drugs lacking data related to safety or efficacy in these populations. The DAP, which requires trial sponsors to plan for diverse trial enrollment, and to articulate the rationale for their plan and the mechanisms to achieve it, will ultimately move the needle towards achieving diverse trial enrollment.

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[1] Kanapuru B, Fernandes LL, Baines A, Ershler R, Bhatnagar V, Pulte E, Gwise T, Theoret MR, Pazdur R, Fashoyin-Aje L, Gormley N. Eligibility criteria and enrollment of a diverse racial and ethnic population in multiple myeloma clinical trials. Blood. 2023 Jul 20;142(3):235-243. doi: 10.1182/blood.2022018657. PMID: 37140031

[2] Aldrighetti CM, Niemierko A, Van Allen E, Willers H, Kamran SC. Racial and Ethnic Disparities Among Participants in Precision Oncology Clinical Studies. JAMA Netw Open. 2021 Nov 1;4(11):e2133205. doi: 10.1001/jamanetworkopen.2021.33205. PMID: 34748007; PMCID: PMC8576580

[3] U.S. Food and Drug Administration. Drug trials snapshots summary report; 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

[4] Unger, J. M., Hershman, D. L., Osarogiagbon, R. U., Gothwal, A., Anand, S., Dasari, A., Overman, M., Loree, J. M., & Raghav, K. (2020). Representativeness of Black Patients in Cancer Clinical Trials Sponsored by the National Cancer Institute Compared With Pharmaceutical Companies. JNCI Cancer Spectrum, 4(4), pkaa034 https://doi.org/10.1093/jncics/pkaa034

[5] Loree, J. M., Anand, S., Dasari, A., Unger, J. M., Gothwal, A., Ellis, L. M., Varadhachary, G., Kopetz, S., Overman, M. J., & Raghav, K. (2019). Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018. JAMA Oncology, 5(10), e191870. https://doi.org/10.1001/jamaoncol.2019.1870

[6] https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

We offer comments on the following guidance provisions:

Generalizable data vs differential safety and efficacy

There are two main scientific rationales to pursue representative trial enrollment, with different strategies needed to achieve them: (1) so that the overall findings of the trial are generalizable to the entire population; and (2) to identify potential differential effects of the drug being tested in different racial or ethnic subgroups. The Guidance is unclear on which of these rationales should drive the DAPs. Although the Guidance states that the DAP goal is to increase enrollment of historically underrepresented populations to improve generalizability of the findings to the target populations, the Guidance also states that it may be necessary to increase proportional enrollment of certain subpopulations in order to characterize differential efficacy or safety, or other clinical measures.

In the Drug Trials Snapshot Report for 2023, the 14 approved cancer drugs had an average trial size of fewer than 325 patients, with the largest trial at just over 1,000 patients, and the smallest only 65.[3] Clearly these trials are not powered to understand subgroup differences, and FDA notes that in the case of some rare diseases, "Despite enrolling a representative population in that study, participant numbers may be small, potentially precluding the detection of any differences in safety and effectiveness across the study population, should they exist, or limiting the sponsor's ability to conduct a robust assessment of observed differences. However, consistent representative enrollment may provide opportunities for hypothesis generation and further study." The guidance would benefit from more detail regarding the considerations that would lead to studies being designed to power the detection of subgroup differences versus when they should be designed for basic representation. Factors may go beyond simple disease incidence to include prior study results, biologic mechanisms of action, etc. **We encourage FDA to add clarity around when DAPs should be structured to meet the generalizability versus differential safety or efficacy goals, with consideration for achievable enrollment targets**.

Balancing pre- and post-marketing requirements

This Guidance does not address consequences for failing to meet the enrollment goals in the DAP, but as FDA considers enforcement mechanisms, we believe that there are precedents in existing approval pathways. The accelerated approval pathway is available for drugs for a serious condition that could provide a meaningful improvement over existing therapies. For these drugs, FDA may allow approval based on a surrogate endpoint (e.g. biomarkers or imaging) that can be measured quickly and might predict long-term clinical benefit (e.g. survival) rather that holding approval until the more time-consuming endpoints like survival are available. For these accelerated approvals, the sponsors must commit to measuring these long-term outcomes in a clinical trial, and trials to do so must generally be underway at the time of accelerated approval.

Similarly, we believe that FDA should offer more flexibility in meeting DAP trial enrollment goals for rare diseases and diseases that are serious and life-threatening, such as cancer, when a new therapy offers meaningful improvements in patient outcomes. That is not to suggest that these diseases should be exempt

from meeting DAP goals, but rather the benefits of the therapy should not be withheld from the public once a drug's general efficacy has been shown. Instead, we recommend that FDA consider mechanisms to ensure that appropriate representation is achieved in the combined pre- and post-market space.

We encourage FDA to consider pre- and post-marketing data requirements for therapies for serious and life-threatening diseases when the therapy offers meaningful improvements over existing therapies.

The global nature of oncology trials

The draft Guidance states that the DAP requirement applies to all trials, and that multinational trials should account for the need to enroll populations representative of the U.S. target population. It is specified that this requirement holds even when local population descriptors are absent or different from those used in the U.S. Global and U.S. populations with the same label may be not only genetically different but also have very different extrinsic factors that affect disease risk and prevalence such as diet, lifestyle, comorbidities, and access to health care. **We ask FDA to add more detail to the guidance on how non-U.S. populations should be characterized in enrollment goals and how they factor into representativeness.**

Racial/ethnic category expansion and disaggregation

We support the draft Guidance's encouragement of considering broad factors such as geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and co-morbidity as part of DAP racial and ethnic demographic characteristics. Similarly, while many of the racial categories are flawed, we applaud the encouragement for sponsors to include more detailed race and ethnicity data beyond the Office of Management and Budget's (OMB) categories. For example, the broad category of "Asian-American" could encompass individuals with a wide range of ancestry.

Ensuring detailed race and ethnicity data are available, as well as accurate, objective and impartial, is critical to evidence-based health equity work while also ensuring there are strong privacy protections around the collection of these data. ACS CAN supports policies that promote the timely collection and publication of demographic data that aid researchers in identifying disparities to improve health equity in cancer prevention, detection and treatment. Adding subgroups to the required minimum reporting categories can provide opportunities for improved reporting of information pertaining to the health of diverse U.S. population. **These elements, along with the pending incorporation of updates to the OMB Directive No. 15, will help sponsors to better identify and characterize population groups and subgroups to ensure equitable representation in clinical trials**.

Intersectionality of demographic variables and additional categories

DAPs must include goals broken down by race, ethnicity, sex, and age. The guidance, however, does not discuss how the intersection of multiple demographic variables would be considered. For example, would it be permissible if the preponderance of elderly participants came from only one demographic group/one country, or if the male to female ratio within groups was heavily skewed so long as the overall ratio were correct? **The guidance would benefit from more clarity on assessing multiple overlapping demographic variables.** Beyond race, ethnicity, sex, and age, factors such as geographic location, gender identity, sexual

orientation, and socioeconomic status contribute to health disparities and can act as barriers to trial enrollment. **We are therefore supportive of FDA's encouragement to factor these elements into the development of DAPs.**

Barriers to trial participation

Setting categorical enrollment goals is an important foundational step to achieving representation in clinical trials. However, goals without implementation plans are unlikely to succeed. Our research shows that, in oncology, structural issues outside a patient's control are the overwhelming cause of low and unequal trial participation.[7,8] Specific trial design and infrastructure elements such as inclusion/exclusion criteria, where trials are offered, whether providers screen and refer patients, and participant burdens (e.g., costs, time, travel needs) lead to low or inequitable trial enrollment. **We support the requirement for sponsors to specify measures to address disparities and barriers to facilitate patient enrollment and participation.**

FDA–ACS Symposium

Together with FDA, the American Cancer Society and ACS CAN are cohosting a symposium in October 2024 entitled *Benchmarks for Diversity in Oncology Clinical Trials* to provide insight into best practices for creating effective diversity action plans. Topics at the meeting will include assessing appropriate data sources; statistical methods for interpreting prevalence/incidence and application to creating a DAP; and approaches such as decentralized trials and digital health strategies to facilitate enrollment of participants. Findings from the meeting will directly inform a number of the areas listed above. **We encourage FDA to incorporate findings and recommendations from this symposium into the final Guidance**.

Conclusion

We support FDA's Guidance on required DAPs for phase three or pivotal trials, in which sponsors specify their goals, rationale, and strategies to increase the representation of historically underrepresented groups in clinical trial enrollment. We ask the FDA to consider leveraging post-market studies as a tool to augment collection of data from diverse trial participants when trial sizes or degree of unmet need make complete collection of such data in the premarket setting difficult. We also suggest additional clarification in the final Guidance on when powered subgroup analyses are appropriate, how to characterize global populations for enrollment targets that represent U.S. racial and ethnic diversity, and we encourage incorporation of the findings from the upcoming FDA–ACS *Benchmarks for Diversity in Oncology Clinical Trials* meeting.

Thank you for the opportunity to comment on Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies: Draft Guidance for Industry. If you have any

[7] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. J Natl Cancer Inst. 2019 Mar 1;111(3):245-255. doi: 10.1093/jnci/djy221. PMID: 30856272; PMCID: PMC6410951.

[8] Unger JM, Hershman DL, Till C, Minasian LM, Osarogiagbon RU, Fleury ME, Vaidya R. "When Offered to Participate": A Systematic Review and Meta-Analysis of Patient Agreement to Participate in Cancer Clinical Trials. J Natl Cancer Inst. 2021 Mar 1;113(3):244-257. doi: 10.1093/jnci/djaa155. PMID: 33022716; PMCID: PMC7936064

questions, please feel free to contact me or have your staff contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

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President
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