June 13, 2022

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
Docket No. FDA-2021-D-0789
5360 Fishers Lane
Room 1061
Rockville, MD 20852

**Re: FDA-2021-D-0789: Diversity Plans To Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials**
87 FR 22211 (April 14, 2022)

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on the Diversity Plans To Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials Draft Guidance for Industry (Guidance). ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. We empower advocates across the country to make their voices heard and influence evidence-based public policy change, as well as legislative and regulatory solutions that will reduce the cancer burden. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is critical to the fight for a world without cancer.

We commend the Administration for recognizing the importance of enrolling representative numbers of participants from underrepresented racial and ethnic populations in the U.S. in clinical trials. The Guidance coincides with several legislative efforts to improve clinical trial diversity and is an important step toward realizing the goal 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 than for clinical trials in other disease areas.

Clinical trials are an essential step in advancing potential new treatments that improve outcomes for people with cancer. Before any new treatment moves from the research setting to the patient, trials must enroll a sufficient number of participants to assess a treatment's

American Cancer Society Cancer Action Network, Inc.
655 15th Street, NW, Suite 503, Washington, D.C. 20005
202.661.5700
fightcancer.org

safety and efficacy. Although most cancer patients offered a clinical trial will participate, adequate enrollment is an ongoing challenge due to provider/institutional, patient, and trial design barriers that can reduce patient enrollment. [1,2] The impact of these barriers do not affect all groups equally, which contributes to disparities in trial enrollment and can lead to a trial population that does not represent the U.S. population diagnosed with cancer. While not all trial participation barriers are addressed in the Guidance, they ultimately affect the ability to achieve diverse enrollment. ACS CAN is working to address these issues through a variety of venues including legislative advocacy.

Compared to their cancer burden, some racial and ethnic minority populations in the U.S. are vastly underrepresented in cancer clinical trials that support new drug approvals. For example, from 2008 to 2018, the overall proportion of Black patients was less than 3% in global, pivotal trials supporting new U.S. Food and Drug Administration (FDA) cancer drug approvals. [3] Notably, during this time Black individuals represented 12.1% of the U.S. cancer population. [3] 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. [4] One key driver of the lack of representation of U.S. racial and ethnic minority 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 2020 showed that among the 4,922 patients that participated in trials that led to the approvals of 18 new oncology drugs, only 41% - less than half - were from sites in the U.S. [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 one 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*. 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.

***Elements of the Diversity Plan***

The Guidance recommends that Race and Ethnicity Diversity Plans (Diversity Plans) include a specific plan of action to enroll and retain diverse participants, including a description of specific strategies. Two barriers that can affect the diversity of who enrolls in a trial are the cost of trial participation and the availability of local trials. Patients making less than $50,000 are nearly 30% less likely to enroll in clinical trials. [6] While most insurers are required to cover the

direct medical or "routine costs" of treatment ordinarily administered absent a clinical trial, patients are frequently responsible for non-medical expenses such as transportation and lodging associated with their enrollment. These costs disproportionately affect underrepresented U.S. racial and ethnic populations.[7] While some trial sponsors provide financial support for non-medical costs, those that do not often cite concerns about running afoul of federal anti-kickback prohibitions that could subject them to civil monetary penalties. We commend FDA for acknowledging stakeholder support for financial reimbursement of non-medical expenses incurred by participation in a clinical trial as a means to ensure more diverse participation and for recognizing that this type of reimbursement does not raise issues regarding undue influence.

A second key barrier for patient participation is related to local trial availability. It is estimated that 77% of patients will not have a local trial available for their cancer.[2] We thank FDA for highlighting strategies such as the use of local providers, local laboratories/imaging, and telehealth. Such strategies are key to enabling decentralized clinical trials that can reduce barriers associated with traveling to a trial site that may be at an increased distance or inconvenience compared to a patients regular care. We encourage FDA to issue permanent guidance on the conduct of decentralized trials.

***Global Nature of Oncology Trials***

FDA allows data from trials conducted globally so long as regulations governing ethical treatment of subjects and data integrity are followed. In oncology, close to two-thirds of clinical trial participants in U.S. drug approval applications come from outside the U.S., where the demographic makeup is significantly different.[8] This reality affects the ability to realize diverse representation of U.S. racial and ethnic minorities in cancer trials and also raises questions around what defines representation. For example, are Asians living in Asia that are included in the overall trial population considered the same as Asian Americans or Africans in Africa for African Americans from the standpoint of trial representation? While intrinsic factors like genetics may be similar across nations, extrinsic factors like diet, lifestyle, comorbidities, and access to health care would not reflect those of the U.S. population. Differential outcomes may be more related to these extrinsic factors. The Guidance is unclear to whether Diversity Plans are only applicable to U.S.-based trials or trials in aggregate. We request that FDA clarify its intent.

***Sample Size***

The Guidance acknowledges the increasing reliance on small studies to expedite the development and approval of medical products. This is particularly applicable to cancer trials which often have a small total enrollment in pivotal trials. For example, of 127 clinical trials that supported 92 novel cancer drugs approved by FDA between 2000 to 2016, the median number of trial participants was 191.[9] Comparatively, FDA approved 35 new cardiometabolic drugs

between 2008 to 2017 in which the median number of participants across 143 trials was 5,930, over thirty times larger than in cancer clinical trials.[10] We agree with the Guidance that specific approaches are needed to both obtain data in diverse populations and facilitate efficient medical product development and approval.

***Analytical Plan***

Research has found that intrinsic genetic variation in factors responsible for metabolizing or transporting drugs may drive some differences in safety or efficacy. Currently, there are no FDA requirements for cancer therapeutics entering clinical trials to include appropriately powered subgroup analysis by race or ethnicity for differences in safety or efficacy. We agree with the Guidance that enrollment of racial and ethnic populations based on epidemiology alone may not be sufficient to detect any differences in safety and effectiveness or allow for such inferences. In order to assess subgroup differences, clinical trials must be explicitly designed for that purpose and have an adequate number of participants to detect any difference between subgroups. We support the recommendation that when data indicate that a medical product may perform differentially across the population based on factors associated with race or ethnicity, Diversity Plans should specify study design features that will support analyses to inform the safety and effectiveness of medical products in the relevant racial and ethnic populations. This may require participation of racial or ethnic populations greater than the proportion of overall disease burden.

***Genetic Ancestry***

We agree with the Guidance that racially and ethnically defined populations are often genetically heterogeneous which may make it difficult to discern differential effects due to pharmacogenomic variability. Race and ethnicity are social constructs, and although different groups have been shown to have disparate responses to therapies, genetic ancestry is often a better predictor of pharmacogenomic variability. However, epidemiological data available for research are mostly categorized based on race, region, and ethnicity, which are typically self-reported values that do not directly correspond to genetic ancestry. Therefore, to understand potential differences in safety or efficacy by race and ethnicity, it is important to include diverse participants.

***Category Disaggregation***

Data grouped by race and ethnicity can highlight cancer disparities along the continuum of cancer care starting from research to survivorship. However, aggregating heterogenous racial and ethnic subpopulations in the collection of public health data can obscure health disparities and, in the context of clinical trials, pharmacogenomic-linked variability. The current Office of Management and Budget (OMB) categories for race and ethnicity as outlined in *Directive No. 15 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity* are not homogenous. The U.S. population has continued to become more racially and ethnically diverse since OMB's last revision of these standards. We recommend FDA encourage sponsors to

provide more detailed race and ethnicity data in Diversity Plans beyond the minimum OMB categories for race and ethnicity.

***Reference Data***

The Guidance encourages sponsors to leverage various data sources to set enrollment goals, and if not feasible, enrollment goals may be based on demographics in the overall population with the disease or condition. The availability and concordance of timely, accurate epidemiologic cancer data may vary between sources. While we recognize that various data sources may be needed to accurately set enrollment goals, we recommend FDA provide additional clarity related to the expectations of reference data sets used to determine disease prevalence in underrepresented racial and ethnic populations.

***Applicability to Post-Marketing Studies***

Though the focus of this guidance is on pre-approval trials, we encourage extending this guidance to post-marketing surveillance (Phase IV) studies that are agreed to or required by sponsors. Any disparities between pre-approval demographic breakdowns and post-marketing real-world use and associated outcomes would be important to review.

Thank you again for the opportunity to provide comments, and we look forward to working with you to make sure cancer clinical trials are more diverse and representative of the U.S. population with cancer. If you have any questions, please do not hesitate to contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

Lisa A. Lacasse, MBA
President
American Cancer Society Cancer Action Network

---

[1] Loree JM, Anand S, Dasari A, et al. Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018. JAMA Oncol. 2019;5(10):e191870. doi:10.1001/jamaoncol.2019.1870

[2] Barriers to Patient Enrollment in Therapeutic Clinical Trials. American Cancer Society Cancer Action Network. (2019) Accessed May 30, 2022, from https://www.fightcancer.org/sites/default/files/National%20Documents/Clinical-Trials-Landscape-Report.pdf

[3] 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

[4] 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 On cology, 5(10), e191870. https://doi.org/10.1001/jamaoncol.2019.1870

[5] U.S. Food and Drug Administration. Drug trials snapshots summary report; 2020. https://www.fda.gov/media/145718/download. Accessed May 21, 2022.

[6] Unger, J. M., Gralow, J. R., Albain, K. S., Ramsey, S. D., & Hershman, D. L. (2016). Patient Income Level and Cancer Clinical Trial Participation: A Prospective Survey Study. JAMA oncology, 2(1), 137–139. https://doi.org/10.1001/jamaoncol.2015.3924

[7] Hamel, L. M., Penner, L. A., Albrecht, T. L., Heath, E., Gwede, C. K., & Eggly, S. (2016). Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. Cancer control : journal of the Moffitt Cancer Center, 23(4), 327–337. https://doi.org/10.1177/107327481602300404

[8] 2015-2019 DRUG TRIALS SNAPSHOTS SUMMARY REPORT Retrieved May 26, 2022, from https://www.fdanews.com/ext/resources/files/2020/11-09-20-DrugTrialSnapshotReport.pdf?1604963880

[9] Ladanie, A., Schmitt, A. M., Speich, B., Naudet, F., Agarwal, A., Pereira, T. V., Sclafani, F., Herbrand, A. K., Briel, M., Martin-Liberal, J., Schmid, T., Ewald, H., Ioannidis, J. P. A., Bucher, H. C., Kasenda, B., & Hemkens, L. G. (2020). Clinical Trial Evidence Supporting US Food and Drug Administration Approval of Novel Cancer Therapies Between 2000 and 2016. JAMA Network Open, 3(11), e2024406. https://doi.org/10.1001/jamanetworkopen.2020.24406

[10] Khan, M. S., Shahid, I., Siddiqi, T. J., Khan, S. U., Warraich, H. J., Greene, S. J., Butler, J., & Michos, E. D. (2020). Ten -Year Trends in Enrollment of Women and Minorities in Pivotal Trials Supporting Recent US Food and Drug Administration Approval of Novel Cardiometabolic Drugs. Journal of the American Heart Association, 9(11). https://doi.org/10.1161/JAHA.119.015594