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PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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June 6, 2022

Lauren K. Roth, JD
Associate Commissioner for Policy
Office of the Commissioner
Food and Drug Administration
19903 New Hampshire Avenue
Building 32, Room 4239
Silver Spring, MD 20993-0002

RE: Docket No. FDA–2021–D–0789 for "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials."

Dear Ms. Roth,

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Draft Guidance for Industry, "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinicals," published in the *Federal Register* on April 14, 2022.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

PRIM&R believes the FDA's draft guidance represents a significant and welcome step forward in enhancing diversity in clinical trial participation. We applaud the agency's deliberate efforts to assist industry in advancing this important societal goal by recommending concrete strategies for developing comprehensive diversity plans.

Below are additional recommendations that we believe will not only enhance diversity in clinical trial participation but will also bolster public trust and confidence in scientific research.

PRIM&R recommends that the guidance be reframed to explicitly acknowledge that the constructs of race and ethnicity are scientifically relevant only as proxies or surrogate markers for other demographic characteristics that are more salient to health outcomes, such as

neighborhood, education, employment, access to healthcare, etc. In the current draft, this important point is noted merely as a footnote (Footnote 3), which acknowledges that race and ethnicity are socio-political constructs "and should not be interpreted as being scientific or anthropological in nature." Yet, the details of the guidance fall back on the outdated assumptions of race and ethnicity as genetic markers and reinforce the idea that race and ethnicity are biological variables. **Using "self-identified" race and ethnicity (instead of using OMB defined categories) may better capture the social determinants of health, which are largely ignored in the draft guidance**. In addition, there are other contextual social and environmental factors that intersect with race and ethnicity and impact health outcomes, such as household income, primary language, immigration status, violence, and perceived discrimination.[1] Thus, the FDA should urge sponsors to consider key sociodemographic factors such as those identified by Wilkins, Schindler, & Morris.[2] Furthermore, the guidance should explicitly state that any planned sub-analyses by race and ethnicity should be based on a scientific hypothesis or a strong rationale for potential differences across these domains, which, as mentioned above, are not biological markers.

The reframing should also explicitly **situate the issue of improving enrollment of participants from underrepresented racial and ethnic population as falling under the ethical principle of justice**. PRIM&R was pleased to see that the guidance's justification for increasing diversity of clinical participation is not based solely on concerns of scientific generalizability but recognizes that such non-representativeness reflects broader injustice in access to health care. However, regaining and maintaining public trust and confidence in medical research requires acknowledging the injustice of denying significant parts of the population the benefits of participating in research. We urge the FDA to acknowledge that distrust in clinical research stems not only from historical abuses such as those of PHS Tuskegee Study of Untreated Syphilis, as mentioned in the guidance, but also from current inequities regarding access to, and clear and relevant information about, clinical research and its benefits.

The guidance should offer more robust recommendations for decreasing the burdens of participating in clinical trials. Sponsors should be encouraged to put in place mechanisms that facilitate the participation of individuals without health insurance and who cannot afford trial costs, for example: offering to reimburse travel costs or provide payment for participation, covering the costs of the study drugs themselves as well as the administrative costs associated with providing and taking the study drug, and the costs associated with interventions considered standard of care that may be part of the study. Such measures will ensure that those without health insurance will be able to afford trial participation, which in turn will increase diversity of clinical trial populations. With regard to the ethics of payment to research subjects, PRIM&R recommends that the FDA consider incorporating guidance issued by the Secretary's Advisory Committee on Human Research Protections, which addresses ethical concerns regarding offers of payment to research subjects.[3]

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[1] https://health.gov/healthypeople/priority-areas/social-determinants-health

[2] Wilkins CH, Schindler SE, Morris JC. Addressing Health Disparities Among Minority Populations: Why Clinical Trial Recruitment Is Not Enough. JAMA Neurol. 2020 Sep 1;77(9):1063-1064. doi: 10.1001/jamaneurol.2020.1614. PMID: 32539100; PMCID: PMC7983552.

[3] https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-september-30-2019/index.html

In recent years, the FDA has issued guidance regarding the importance of considering diversity in terms of a range of demographic characteristics, but none resemble the current guidance's recommendation to include a detailed diversity plan. **Thus, we hope that in the future, the FDA will issue additional guidance, similar to the current draft, that will offer recommendations for developing diversity plans for other demographic variables and historically underrepresented populations.**

Finally, while PRIM&R appreciates that in the absence of a statutory basis, the FDA is constrained in its ability to issue mandatory requirements, we are concerned that the nonbinding nature of the recommendations render them ineffective in truly advancing the stated goal of enhancing diversity in clinical trial enrollment. Given costs associated with the work needed to increase diversity in clinical trial enrollment, industry has little, if any, incentive to follow this guidance. Thus, **PRIM&R urges the FDA to consider some of the recommendations set forth in the recent NASEM report, *Improving Representation in clinical trials and Research Building Research Equity for Women and Underrepresented Groups,*[4] as a path to ensuring clinical trial diversity in the future,** including:

- The Department of Health and Human Services (HHS) should establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies, including the Food and Drug Administration (FDA), …. This task force should be charged with the following:
    a. Producing an annual report to Congress on the status of clinical trial and clinical research enrollment in the United States, including the number of patients recruited into clinical studies by phase and condition; their age, sex, gender, race, ethnicity, and trial location (i.e., where participants are recruited); their representativeness of the conditions under investigation; and the research sponsors.
    b. Making data more accessible and transparent throughout the year, such as through a data dashboard that is updated in real time.
    c. Determining what "representativeness" means for protocols and product development plans.
    d. Developing explicit guidance on equitable compensation to research participants and their caregivers, including differential compensation for those who will bear a financial burden to participate.

- The FDA should require study sponsors to submit a detailed recruitment plan no later than at the time of Investigational New Drug and Investigational Device Exemption application submission that explains how they will ensure that the trial population appropriately reflects the demographics of the disease or condition under study and that provides a justification if these enrollment targets do not match the demographics of the intended patient population in the United States.

[4] National Academies of Sciences, Engineering, and Medicine. 2022. *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26479.

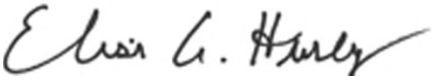
- The Office of Human Research Protections (OHRP) and the FDA should direct local institutional review boards (IRBs) to assess and report the representativeness of clinical trials as one measure of sound research design that it requires for the protection of human subjects. Representativeness should be measured by comparing planned trial enrollment to disease prevalence by sex, age, race, and ethnicity in the trial location (i.e., where participants are recruited). Protocols in which the planned enrollment diverges substantially from disease prevalence should require justification. The OHRP and FDA should establish a plan for remediation for local IRBs that frequently approve protocols that are not representative.

- Federal regulatory agencies, including OHRP, NIH, and FDA, should develop explicit guidance to direct local IRBs on equitable compensation to research participants and their caregivers. In recognition that research participation may pose greater hardship or burdens for historically underrepresented groups, the new guidance should encourage and allow for differential compensation to research participants and their caregivers according to the time and financial burdens of their participation. Differential compensation may include additional reimbursement for expenses including but not limited to lost wages for those with lower socioeconomic status (SES), transportation costs, per diem, dependent care, and housing/lodging, where applicable.

- All sponsors of clinical trials and clinical research (e.g., federal, foundation, private and/or industry) should ensure that trials provide adequate compensation for research participants. This compensation may include additional reimbursement for expenses including but not limited to lost wages for lower SES participants and family caregivers, transportation costs, per diem, dependent care, and housing/lodging where applicable.

Thank you again for the opportunity to comment on the draft guidance. We hope our comments will be useful to the FDA in its ongoing deliberations on this important issue. PRIM&R stands ready to provide any further assistance or input that might be of use. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Sincerely,



Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors