Alliance FOR AGING RESEARCH
Catalyzing Innovation for Healthy Aging

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Oncology Center of Excellence
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
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Re: FDA–2021–D–0789 Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry

Dear Dr. Fashoyin-Aje,

The Alliance for Aging Research (Alliance) is the leading nonprofit organization dedicated to accelerating the pace of scientific discoveries and their application to vastly improve the universal experience of aging and health. We very much appreciate the Food and Drug Administration's (FDA) updated guidance for sponsors to develop Race and Ethnicity Diversity Plans for clinical trial enrollment among members of underrepresented racial and ethnic populations. While the FDA's 2016 guidance focused on how to collect and present race and ethnicity data in submissions, it assumed that there were adequate numbers of enrollees to collect data on. The current FDA guidance recognizes that sponsors should prospectively define approaches "to generating data for a broader and more diverse population early in the development program" that will "improve the generalizability of results across all patient populations, improve our understanding of the disease and/or medical product under study, and inform the safe and effective use of the medical product for all patients who are expected to use the medical product if approved."[1]

[1] U.S. Food and Drug Administration. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry: Draft Guidance. April 2022. https://www.fda.gov/media/157635/download.

Clinical trials are the primary modality for patients to receive investigational therapies. However, multiple barriers—including limited availability of clinical trial sites, populations served by preferred trial sites, limited outreach to communities of color, and overly restrictive exclusion criteria—have led to the systemic underrepresentation of racial and ethnic minority groups. These health disparities are well documented.[2] Racially and ethnically diverse populations experience systemic barriers to care that are known to lead to poor overall health outcomes. It will take proactive solutions to combat these inequities across the board; improving representation in clinical trials is one piece of the larger puzzle.

Clinical trial diversity

Broadly, the aim of study recruitment should be for a representative number of trial participants to reflect the anticipated real-world populations who will receive treatment. The FDA draft guidance recognizes that there are many barriers to recruiting under-represented minority (URM) participants and attempts to address many of them; however, there are still additional barriers/solutions that could be included for consideration as sponsors form their Race and Ethnicity Diversity Plan.

Medical trust among URM groups

The U.S. healthcare system has a long history of racial and ethnic discrimination in medical research and patient care. This has led to worse health outcomes across the board for URM patients, as trust is a foundational element to the doctor/patient relationship and in a patient's adherence to treatment recommendations.[3] The draft guidance cites the unethical Tuskegee experiments as a source for mistrust of the clinical research system among URM groups; however, a series of studies over 14 years from Katz et al.[4], the *Tuskegee Legacy Project*, surveyed thousands of people across seven cities and found that while Black people were nearly twice as "wary" of participating in research compared to White people, they were just as likely as Whites to self-report willingness to participate in biomedical research. Notably, fear of participation due to knowledge of Tuskegee does not impact willingness to participate in research.

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[2]Flores, Laura; Frontera, Walter; Andrasik, Michelle, et al. "Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials." JAMA Network Open. 19 Feb 2021. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776562

[3] Hall, Mark; Dugan, Elizabeth; Zheng, Beiyao; and Mishra, Aneil, Mishra. "Trust in Physicians and Medical Institutions: What Is It, Can It Be measured, and Does It Matter?" The Milbank Quarterly. Dec 2001. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2751209/pdf/milq_223.pdf

[4] Katz, Ralph V et al. "The Tuskegee Legacy Project: Willingness of Minorities to Participate in Biomedical Research." Journal of Health Care for the Poor and Underserved vol. 17.4. 23 Jan 2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1780164/

This indicates that the academic reliance on Tuskegee as a driver of low participation in clinical trials does not follow from modern real-world findings. While the study represents a horrific tragedy perpetrated on the Black community, its impact on modern day URM in clinical trial participation is greatly exaggerated. FDA, sponsors, and scientific institutions should avoid using the experience of Tuskegee as a reason to excuse lack of effort in effective community engagement and addressing barriers to clinical trial access. It is important to address the barriers to clinical trial enrollment that URM communities face today to make significant changes to disparities in clinical trials. In fact, recent studies have found that URM populations do proportionately enroll in clinical research "when a reasonable effort is made to enroll them."[5] Strategies that could constitute a "reasonable effort" are outlined below.

Diversity within these communities

While the Alliance recognizes that the draft guidance is not focused on subcategories within racial and ethnic communities, it is important to note that there are additional exclusionary factors that may limit enrollment or appropriate representation in clinical trials. A study by Hansen, et al. interviewed Black members of a senior center to identify patterns in their thinking about healthcare. The most common theme that emerged from these interviews was "the added insult of ageism."[6] The study found that ageism cuts across sociocultural and racial divisions, "to become the preeminent defining barrier to health care communication."[7]

Therefore, the Alliance recommends that sponsors be required by the FDA to develop strategies for the inclusion of subpopulations within URM communities. These subcategories can include age, gender, multiracial participants, and ethnicities not identified in the US census. This will allow physicians to make the most informed recommendations and find the best therapeutic devices for their specific patients, especially in the growing area of precision medicine. It should also be noted that negative social determinants of health often cause earlier age at disease onset in URMs, which may not be captured in inclusion criteria.

Additionally, the National Institute on Aging at the National Institutes of Health (NIH), the Centers for Disease Control and Prevention, and the Administration for Community Living are collaborating on the Recruiting Older Adults into Research (ROAR) project to encourage older adults and their family caregivers, including under-represented populations, to consider participating in research. Strategies

[5] Ibid.
[6] Hansen, Bryan; Hodgson, Nancy; and Gitlin, Laura. "It's a Matter of Trust: Older African Americans Speak About Their Health Care Encounters." 9 Feb 2015. https://pubmed.ncbi.nlm.nih.gov/25669876/
[7] Ibid.

outlined within the ROAR project materials include educating patients on why research is important to healthy aging, what volunteers need to know about research studies, how older adults can make a difference by participating, and easy initial steps to take to get involved.[8] This effort to engage and educate a relevant subpopulation has easy and actionable items/strategies for increasing clinical trial diversity. The Alliance recommends that sponsors be made aware of relevant resources such the ROAR toolkit.

Staff diversity

Representation in clinical trials is supported by the development of clinical trial investigators that are representative of the communities they serve. Developing a diverse pool of investigators and staff is a necessary step to take in the recruitment of URMs for clinical trials. Racially and ethnically diverse investigators and staff can serve as community ambassadors, increase trust among potential study participants, and ensure that clinical trials are culturally competent and empathetic. According to research from the Tufts Center for the Study of Drug Development, "clinical trials with higher racial and ethnic diversity among staff members saw that increase reflected in the patients they enrolled. Sites with higher levels of staff diversity were also more likely to report that they viewed diversity as a critical aspect of success and incorporate mission statements, operating procedures, and training programs to reinforce diversity awareness and importance."[9] The National Institute for Diabetes and Digestive and Kidney Diseases has been on the forefront of recognizing and investing in representative investigators through their Network of Minority Health Research Investigators (NMRI) initiative, now in its 20th year of operation, which includes active mentorship opportunities.[10] Additional support should be focused to expand programs such as the NMRI, the FDA should evaluate the impact of incorporating diversity requirements or guidelines for clinical trial staff and study designers, and sponsors should implement strategies for the recruitment and retention of URM investigators.

Accessibility

A major barrier for securing diversity within clinical trials is the ease and accessibility for potential participants to engage in the study. Most clinical trials are conducted at major university hospitals

[8] National Institute on Aging. "Recruiting Older Adults into Research (ROAR) Toolkit." https://www.nia.nih.gov/health/recruiting-older-adults-research-roar-toolkit
[9] Tufts University School of Medicine. "To Increase Diversity in Clinical Trials, First Increase Staff Diversity." 3 Dec 2021. https://medicine.tufts.edu/news-events/news/increase-diversity-clinical-trials-first-increase-staff-diversity
[10] National Institute of Diabetes and Digestive and Kidney Diseases. "Network of Minority Health Research Investigators." https://www.niddk.nih.gov/research-funding/research-programs/diversity-programs/network-minority-health-research-investigators-nmri

and urban centers, according to a study by Seidler et al., which found that within a region, population density, availability of healthcare and/or social service facilities, and the number of full-time educational establishments together were strong predictors of the number of clinical trial sites per region.[11] With the rise in telemedicine, there is potential for many more clinical trials to be decentralized. Remote clinical trial participation has been found to be associated with increased equity of research and inclusion of participants from diverse racial, ethnic, and geographic communities.[12] Digital experiences also provide opportunities for data gathering and clinical trial recruitment, including via targeted social media campaigns. However, it is important to note that telemedicine and decentralized clinical trials do not automatically correlate with increased diversity of test populations, they just provide increased opportunity for recruitment. Therefore, it is important that decentralized trials are designed with a specific focus on health equity.

Similarly, a recent survey study found that the patients with annual household incomes below $50,000 were less likely to participate in a cancer clinical trial than those with higher outcomes, and participation rates fell further when households reported smaller annual incomes. Households who reported annual incomes of less than $20,000 had the lowest participation rate in these trials.[13] US Census Data shows that URM have consistently been over-represented among the US population in poverty.[14] In 2019, Black Americans represented 13.2 percent of the total US population, but 23.8 percent of the population living in poverty, and statistics for non-white Hispanics was similar.

Therefore, a focus on the recruitment of trial participants from low-income communities is necessary for increasing clinical trial diversity, and study design should make the trial as financially accessible as possible. While Medicare and Medicaid are required to cover the routine medical costs of trials, there are many other factors that can make trials a financial strain for potential participants. These can include time taken off work, the need to travel far distances, transportation and parking expenses, and an increased number of doctors' visits. This disparity undermines trial results and perpetuates preexisting health inequities. Some major strategies for recruiting low-income racial/ethnic minorities include repeated contact with potential participants, community

[11] Seidler, Elizabeth M.; et al. “Geographic distribution of clinical trials may lead to inequities in access.” Clin Invest 4 no. 4: 373-80. 2014. https://www.openaccessjournals.com/articles/geographic-distribution-of-clinical-trials-may-lead-to-inequities-in-access.pdf
[12] Stewart, Jenell; Krows, Meighan; Schaafsma, Torin; et al. “Comparison of Racial, Ethnic, and Geographic Location Diversity of Participants Enrolled in Clinic-Based vs 2 Remote COVID-19 Clinical Trials.” JAMA Network Open. 19 Dec 2021. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789002
[13] National Cancer Institute. “Low Income is a Barrier to Clinical Trial Enrollment, Study Suggests.” 16 Nov 2015. https://www.cancer.gov/news-events/cancer-currents-blog/2015/income-trials
[14] United States Census Bureau. “Inequalities Persist Despite Decline in Poverty for All Makor Race and Hispanic Origin Groups.” 15 Sep 2020. https://www.census.gov/library/stories/2020/09/poverty-rates-for-blacks-and-hispanics-reached-historic-lows-in-2019.html

partnership, and culturally sensitive recruitment staff (as mentioned above).[15] Sponsors should also consider tracking or proactively finding out methods of payment for ancillary trial costs, such as hotel stays.

The US Census Bureau also reports that low-income households are significantly less likely to have insurance coverage, and therefore to have access to the specialty practitioners who typically refer patients for clinical trials. Sponsors should consider finding ways to reach patients who may not be insured.

Lastly, sponsors of trials should ensure that trial participants are guaranteed access to medical interventions following the end of the trial, should the medication or device prove effective and continued use prove necessary for trial participants.

Engaging community leaders and patient advocacy organizations

Trust is imperative when communicating new information or addressing misconceptions within diverse communities. Establishing positive relationships with community leaders is a strong tool for establishing trust. Community leaders can include cultural ambassadors, faith-based organizations, local governments, and learning institutions such as universities and libraries. Trusted messengers can help refer diverse patients for trials and potentially serve as study sites for the trial, bringing the trials directly to the communities most in need of impact and engagement.

Patient advocacy groups (PAGs) and minority health organizations are designed to disseminate information, promote education, and increase awareness for their constituents. Patient advocacy organizations are often able to assist with clinical trial recruitment and are another trusted source of information for patients. Many PAGs have direct access to patients and researchers, making them a resource for meaningful feedback on trial and study design. Involving patients, advocates, and caregivers in the study-design process can ensure that trials are developed in a patient-centered way, proactively address potential barriers to participation, and allow investigators to further establish trust among URM communities. For example, the National Minority Quality Forum has partnered with Microsoft to create a National Clinical Trial Network, an interactive portal and permanent IT infrastructure that enables research investigators to quickly identify minority populations who share a medical need and, when appropriate, facilitate their recruitment into

[15] Cui, Zhaohui; Truesdale, Kimberly; Robinson, Thomas; et al. Recruitment strategies for predominantly low-income, multi-racial/ethnic children and parents to 3-year community-based intervention trials: Childhood Obesity Prevention and Treatment Research (COPTR) Consortium." Trials. 28 May 2019. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3418-0

clinical trials in a timely and cost-efficient manner.

Developing Best Practices

The FDA should be sure to collect information from these Plans so that best practices for recruiting URM populations to trials can be developed. FDA should publish findings on the impact of the Plan, and work to change requirements if sponsors fail to adequately recruit diverse trial participants.

Conclusion

Clinical trials represent the cutting edge of medicine, and ensuring diversity, equity, and inclusion efforts are central to trial design is of paramount importance. Despite important and necessary policy changes such as the FDA and the NIH's mandates on proportional race representation, clinical trials leading to drug approval have not shown improvement in the recruitment and retention of minority populations in the last 15 years.[16] Major barriers to patient recruitment for trials include lack of community trust, patient education and awareness, and prohibitive cost of treatment. It is the hope of the Alliance that the FDA will incorporate this information when considering the requirements and goals for the development of a Race and Ethnicity Diversity Plan.

Thank you for the opportunity to comment on this issue. If you have any questions, please contact Adina Lasser at alasser@agingresearch.org. We look forward to working with you.

Sincerely,

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Vice President of Public Policy and Government Relations

Adina Lasser
Manager of Public Policy

[16] Jayakrishnan, Thejus et al. "Landmark Cancer Clinical Trials and Real-World Patient Populations: Examining Race and Age Reporting." Cancers vol. 13,22 5770. 18 Nov. 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8616211/