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ABC MISSION:

To promote the prevention and treatment of cardiovascular disease including stroke, in Blacks and other minorities and to achieve health equity for all through the elimination of disparities.

June 13, 2022

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Submitted online at:

<https://www.federalregister.gov/documents/2022/04/14/2022-07978/diversity-plans-to-improve-enrollment-of-participants-from-underrepresented-racial-and-ethnic#open-comment>

RE: Diversity Plans To Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability [FDA-2021-D-0789]

Dear Commissioner Califf:

The Association of Black Cardiologists (ABC) appreciates the opportunity to comment on the draft guidance for industry

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials” as published in the *Federal Register* on April 14, 2022.

There are a number of factors that can influence the efficacy and safety of new medicines and medical products, including sex, age, race, ethnicity, lifestyle, and genetic background. Yet, racial and ethnic minorities continue to be underrepresented in cardiovascular and other clinical trials.

Since many clinical algorithms and decision tools rely on data from clinical trials, the lack of representation in clinical databases also contributes to racial bias in clinical decision making, and it can skew decision making about the cost-benefit of therapeutics. Indeed, the failure to achieve diversity in clinical trials has far reaching effects, including the perpetuation of disparities in health care.

The ABC supports expansion of the Food and Drug Administration’s existing guidance — *Collection of Race and Ethnicity Data in Clinical Trials* — by encouraging trial and study

sponsors to submit a Race and Ethnicity Diversity Plan to the investigational new drug application, for a drug, including biological products regulated as drugs, or the investigational device exemption application, for a device. ABC also recognizes that while the FDA can encourage and support sponsors in development of diversity plans, trial sponsors are not currently required to develop or submit these plans. As such, the ABC is on record in support of legislation that would *require* clinical trial sponsors to build in specific, measurable enrollment targets as part of their trial design, prior to Phase II or III trials, to ensure enrollment includes participants reflective of the diverse population affected by a specific disease or condition the therapy or device is intended to address.

Recommended Elements of the Plan

The ABC offers the following comment on some of the FDA's recommended elements of a diversity plan:

#3 Goals for enrollment of underrepresented racial and ethnic participants

As sponsors identify goals for trial enrollment of underrepresented racial and ethnic populations, representation of study subjects in a clinical trial should be reflective, when feasible, of the estimated prevalence in the United States of the disease or condition which a drug is approved to treat, disaggregated by demographic subgroup, including age group, gender, race, and ethnicity. Or, in the case of a medical device, the patient population in the United States expected to use the device, disaggregated in the same manner.

We acknowledge, however, that enrolling subjects in ratios reflective of the population can be difficult to achieve and may not be informative for a particular sub-population. For example, if prevalence of a disease or condition is higher in one subgroup, there may be value in enrolling disproportionate numbers from that subgroup since the subgroup will likely be the group targeted for utilization of the product.

The data derived from clinical studies should be representative of the demographic composition anticipated to receive the treatments. However, use of data obtained from groups that are markedly dissimilar to the demographics present in the United States can broaden the gap of clinical data available to advance health care in America. It is well known that dissimilarities based on race/ethnicity, social positioning/determinants of health, access to health care, as well as cultural factors such as diet, health literacy and therapeutic expectations can markedly vary clinical outcomes of patients undergoing treatment for a specific illness. Data obtained from international sources should be matched to specific U.S. demographic groups for consideration of U.S. approval. For instance, data from Black South Africans may not be generalizable to outcomes in African Americans. As such, it is critically important that when setting enrollment goals that sponsors leverage various data sources (e.g., published literature and real-world data) and set enrollment targets for racial and ethnic populations that are proportionate to the demographic composition of those anticipated to receive a treatment.

*#4 Specific plan of action to enroll and retain diverse participants &
#5 Status of meeting enrollment goals*

ABC supports the recommendation that trial and study sponsors detail the operational measures that will be implemented to enroll and retain under-represented racial and ethnic participants, as well as the planned use of data to characterize safety, efficacy and optimal dosage in these participants, when applicable. We appreciate the FDA has recommended strategies that sponsors can use for trial enrollment and retention, including study site location and access, community outreach, and reducing burdens due to trial/study design/conduct.

As you stated during your remarks at the April 2 ABC Scientific Symposium “CARDIO-JUSTICE: Moving Beyond Health Equity in Cardiovascular Care,” there is a need to get clinical trials into places where people are living, which includes leveraging digital capabilities. As you pointed out, this means creating digital technologies that can be optimized by those who are not yet deeply embedded in the use of technology.

Among key strategies for diverse trial enrollment and retention is effective communication. The ABC was involved with a collaborative study¹ that involved ABC physician members, individuals from a large research-intensive biopharmaceutical company, clinical trial experts, and other key stakeholders to investigate barriers to minority participation in U.S. clinical trials and to identify potential solutions. The study specifically focused on minority patients, referring physicians, investigators who were minority-serving physicians, and trial coordinators. The overall goal was to develop potentially sustainable solutions that would benefit all key stakeholders and lead to making diversity in clinical trials a standard part of the clinical research model.

The study findings emphasized the importance of effective communications across key stakeholders. As part of a diversity plan, sponsors should include plans for collaboration and partnership with key stakeholders, community and civic organizations and leaders, and the faith-based community. These partnerships will help to improve participant trust, and consequently, trial enrollment and retention. Within its recommended strategies, FDA should include among its examples the training of all trial personnel about the importance of diversity and the corresponding scientific and educational rationales and the dissemination of culturally sensitive and health-literate educational materials. To facilitate this, sponsors could incorporate an “Inclusive Clinical Trials Implementation Checklist” (Appendix A). Compliance with a checklist could assist assessing whether a sponsor is meeting or continuing to strive toward its diverse enrollment and retention targets.

Conclusion

Although outside the scope of the draft guidance, the ABC wishes to use this opportunity to provide additional perspective and comment on improving enrollment of participants from

¹ Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G, Regnante JM. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr Probl Cardiol.* 2019 May;44(5):148-172. doi: 10.1016/j.cpcardiol.2018.11.002. Epub 2018 Nov 9. Erratum in: *Curr Probl Cardiol.* 2021 Mar;46(3):100647. PMID: 30545650.

underrepresented racial and ethnic populations.

Historically, diverse clinical trial enrollment has been perceived to add expense due to lengthened study timelines and diminished data quality due to patient non-compliance and site study conduct. A recent study² found cardiovascular research subject diversity may be predicted from site characteristics and enhanced without compromising key study performance metrics.

A gap persists in clinical infrastructure which makes clinical trials outside the academic center difficult. Making grants and other forms of support available to community health centers, including rural health clinics, federally qualified health centers (FQHCs), and Indian Health Service facilities, is needed to increase their capacity to participate in clinical trials and research. Funding should be used to hire necessary personnel, including research nurses and study coordinators, and to develop community engagement strategies and build community partnerships.

Equitable access to clinical trials will not exist until the physicians responsible for the care of diverse patients are engaged with the clinical research process. Oftentimes these clinicians are themselves diverse and struggle with making clinical decisions regarding therapeutic options with limited or no data to support or understand its use and effects in the diverse patient's subgroup. In the current environment, important racial or other demographic differences are often detected if a safety signal arises during post-market surveillance. No conclusive statement regarding medical product efficacy in diverse subgroups is possible due to statistical underpowering from the low sample size.

Ultimately, a 'culture of research' should be developed and supported throughout the medical community to continuously and consistently collect clinical data to guide efforts to advance health care. Efforts must be made to include physicians caring for the diverse communities in the research process. In addition to facilitating clinical research at FQHCs, these efforts will likely include education of trainees and practicing physicians on the research process, post-market surveillance and insights gained from clinical trials regarding race/ethnicity.

Treating physicians are often the gateway to participation in clinical trials. The results of the study published in *Current Problems in Cardiology*³ reinforce the findings of others and of national surveys that physicians are consistently rated as the most trusted source of information for patients. However, physicians, who are often already under significant time constraints, that are worsened by regulatory and administrative burdens, like prior authorization, may lack the time required to explain clinical trials to their patients. They may also be concerned that clinical trial participation may interfere with the physician-patient relationship, and they may lack comfort with obtaining informed consent and/or explaining clinical trials.⁴ Nationally, Medicaid reimbursement rates are about 70 percent of Medicare rates on average, with variation by type of

² Batchelor WB, Damluji AA, Yong C, Fiuzat M, Barnett SD, Kandzari DE, Sherwood MW, Epps KC, Tehrani BN, Allocco DJ, Meredith IT, Lindenfeld J, O'Connor CM, Mehran R. Does study subject diversity influence cardiology research site performance?: Insights from 2 U.S. National Coronary Stent Registries. *Am Heart J.* 2021 Jun;236:37-48. doi: 10.1016/j.ahj.2021.02.003. Epub 2021 Feb 24.

³ Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G, Regnante JM. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr Probl Cardiol.* 2019 May;44(5):148-172. doi: 10.1016/j.cpcardiol.2018.11.002. Epub 2018 Nov 9. Erratum in: *Curr Probl Cardiol.* 2021 Mar;46(3):100647. PMID: 30545650.

⁴ Ibid.

service. A good starting point to help create incentives for treating physicians to direct patients to clinical trials and to ensure that all patients have the same access to potentially cutting edge treatments offered through clinical trials is to improve Medicaid rates, including by setting them on par with Medicare rates. We encourage collaboration between the FDA and the Centers for Medicare and Medicaid Services on other potential ways to incentivize clinicians to make clinical trials accessible to diverse populations.

We appreciate your consideration of ABC's views and suggestions, and we look forward to ongoing collaboration on this important topic. Should you desire additional information or wish to speak with any of ABC member experts, please contact Camille Bonta, ABC policy consultant, at (202) 320-3658 or cbonta@summithealthconsulting.com.

Sincerely,



Anekwe E. Onwuanyi, MD
President
Association of Black Cardiologists



Barbara A. Hutchinson, MD, PhD
Board Chair
Association of Black Cardiologists

TABLE 4. Inclusive clinical trials implementation checklist*.

Building trust	
Do the investigator and trial coordinator have ongoing communications and true partnerships with “trusted” individuals and community groups (eg, providers, community leaders, and faith-based community) in a manner that is effective, transparent, and culturally appropriate for their service area?	✓
Common understanding of the goal	
Do all stakeholders involved in the clinical trial process or recruitment, accrual, and retention understand the goal of attracting and retaining a representative study population?	✓
How does the sponsor demonstrate this commitment throughout the clinical trial process?	✓
Is this information communicated during investigator meetings?	✓
When is this communicated, and how and by whom is it reinforced?	✓
Clinical trial awareness	
Do all key stakeholders involved in the clinical trial process, particularly the patients’ referring physician and trusted community leaders, understand and have comfort with the clinical research process and awareness of resources (available from sponsors, national patient organizations, and local sources) to assess eligibility and participation and consent?	✓
Are all stakeholders able to effectively communicate and reinforce the process of a clinical trial as a treatment option to potential and ongoing participants?	✓
Do all stakeholders have this information in a format that is health literate and accessible?	✓
Optimizing the role of the study coordinator	
Does your program have clarity of the role of designated study coordinator(s) with all stakeholders (importantly, the primary provider care partners and community partners) to ensure understanding of patient situation and new questions so that they can proactively and quickly address situations in a manner that is effective and coordinated?	✓
Does the study coordinator ensure that the appropriate leaders are engaged to thank the patients for their participation throughout the study (before, during and completion)?	✓
Addressing resource and time constraints	
Has the investigator unit had a discussion with sponsor(s) or patient organizations and other local resource sources for anticipated and ongoing support measures for patients (such as travel, housing, parking, and child or elder care)?	✓
Do patients and care partners know to ask the study coordinator about resources available to them in the recruitment stage so that this does not become a barrier to ongoing participation or retention?	✓
* Suggested for use by multiple stakeholders: clinical trial investigators, primary provider, sponsors, health care professionals, trial coordinators, community leaders, patients, and care partners.	

⁵ Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G, Regnante JM. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr Probl Cardiol.* 2019 May;44(5):148-172. doi: 10.1016/j.cpcardiol.2018.11.002. Epub 2018 Nov 9. Erratum in: *Curr Probl Cardiol.* 2021 Mar;46(3):100647. PMID: 30545650.