NATIONAL HEALTH COUNCIL

September 26, 2024

The Honorable Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

RE: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies [Docket No. FDA-2021-D-0789]

Dear Commissioner Califf:

The National Health Council (NHC) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for industry "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies."

Created by and for patient organizations more than 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, equitable, and sustainable health care. Made up of more than 170 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses and organizations representing biopharmaceuticals, devices, diagnostics, generics, and payers.

The NHC has long been committed to advancing diversity in clinical research and has actively engaged its members on this critical issue over time.[1,2,3,4] Ensuring that clinical trial participants represent the broader population is not just a matter of fairness but also of scientific rigor: inclusive trials yield data that is more relevant and reliable across

[1] National Health Council. (2019). Food and Drug Administration's (FDA's) draft guidance on enhancing the diversity of clinical trial populations. Retrieved from https://nationalhealthcouncil.org/wp-content/uploads/2019/12/NHC_Comments_FDA_Clinical_Trial_Eligibility.pdf

[2] Mason, M. (2020). NHC commitment to ensure representativeness in all policy work. Retrieved from https://nationalhealthcouncil.org/blog/nhc-commitment-to-ensure-representativeness-in-all-policy-work/

[3] National Health Council. (2021). Access, affordability and quality: A patient-focused blueprint for real health equity. Retrieved from https://nationalhealthcouncil.org/wp-content/uploads/2022/01/Access-Affordability-and-Quality-A-Patient-Focused-Blueprint-for-Real-Health-Equity.pdf

[4] National Health Council. (2022). NHC comments on FDA diversity in clinical trials guidance. Retrieved from https://nationalhealthcouncil.org/wp-content/uploads/2022/06/NHC-FDA-DICT-Guidance-Comments.pdf

different demographic groups, leading to more accurate and generalizable findings. As part of this ongoing commitment, the NHC convened a virtual meeting on August 5, 2024, to discuss this draft guidance. This meeting, attended by 114 individuals representing 55 NHC member organizations, underscored the strong and sustained interest within our community in promoting health equity and ensuring that clinical research reflects the diversity of the populations it serves. During the meeting, participants were asked to respond to several poll questions to gauge their perspectives on the draft guidance. The results indicated a positive reception, with many respondents describing the guidance as "important," "necessary," and a "good step forward." However, there were also calls for greater clarity and additional information, reflecting the nuanced views of our members and the need for continued dialogue.

The NHC commends the FDA for its efforts to advance health equity through this draft guidance, which represents a step forward in addressing long-standing disparities in clinical trials and enhancing the inclusivity of clinical research. Considering our discussions and our long-standing commitment to this issue, the NHC offers the following comments and recommendations to further refine and strengthen the FDA’s draft guidance on Diversity Action Plans (DAPs) for clinical trials.

General Comments

The NHC strongly supports the FDA's draft guidance requiring DAPs for Phase 3 and other pivotal clinical trials. This guidance is long overdue and comes at a time when there is increasing recognition of the critical importance of inclusivity in public health and medicine. Disparities in clinical trial participation have been well-documented, with certain populations, particularly racial and ethnic minorities, women, pregnant and lactating people, older adults, and people with disabilities, often underrepresented in

clinical research.[5,6,7,8,9,10,11,12,13,14] Enhancing the meaningful representation of diverse participants in clinical trials will lead to studies that more accurately reflect the patient populations most likely to use the product upon regulatory approval. This approach is critical for gathering information on drug response, safety, and efficacy in populations that have been historically underrepresented, ultimately contributing to more equitable health outcomes and improving the overall relevance of trial findings. DAPs will help enhance sponsors' efforts to strategically recruit and retain participants from diverse backgrounds, thereby enhancing the representativeness of clinical trials, improving the overall quality of research, and ultimately leading to better health outcomes for all patients.

Strengths of the Draft Guidance

Recognition of the Importance of Diversity

The draft guidance rightly emphasizes the critical role that diversity and representativeness play in clinical research. By setting clear expectations for the

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[5] Sirugo, G., Williams, S., and Tishkoff, S. (2019). The missing diversity in human genetic studies. *Cell, 177(1)*, 26-31.

[6] Agency for Healthcare Research and Quality. (2021). AHRQ policy on the inclusion of priority populations in research. Retrieved from https://www.ahrq.gov/topics/individuals-special-health-care-needs.html#:~:text=The%20AHRQ%20Policy%20on%20the%20Inclusion%20of%20Priority,and%20justification%20is%20provided%20that%20inclusion%20is%

[7] 20inappropriateRamamoorthy, A., Pacanowski, M., Bull, J., and Zhang, L. (2015). Racial/ethnic differences in drug disposition and response: Review of recently approved drugs. *Clinical Pharmacology & Therapeutics*, 97(3)*,* 263–273.

[8] Scott, P., Unger, E., Jenkins, M., Southworth, M., McDowell, T., Geller, R., Elahi, M., Temple, R., and Woodcock J. (2018). Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *Journal of the American College of Cardiology*, *71(18),* 1960–1969.

[9] Blehar, M., Spong, C., Grady, C., Goldkind, S., Sahin, L., and Clayton, J. (2013). Enrolling pregnant women: Issues in clinical research. *Womens Health Issues, 23(1),* 39–45.

[10] Shields, K. and Lyerly, A. (2013). Exclusion of pregnant women from industry-sponsored clinical trials. *Obstetrics & Gynecology, 122(5)*, 1077–1081.

[11] Vitale, C., Fini, M., Spoletini, I., Lainscak, M., Seferovic, P., and Rosano, G. (2017). Under-representation of elderly and women in clinical trials. *International Journal of Cardiology, 232,* 216–221.

[12] McDonald, K., Schwartz, A., and Sabatello, M. (2022). Eligibility criteria in NIH-funded clinical trials: Can adults with intellectual disability get in? *Disability and Health Journal, 15(4)*: *101368*. doi: 10.1016/j.dhjo.2022.101368

[13] Plosky, W., Ne'eman, A., Silverman, B., Strauss, D., Francis, L., Stein, M., and Bierer, B. (2022). Excluding people with disabilities from clinical research: Eligibility criteria lack clarity and justification. *Health Affairs, 41(10).* https://doi.org/10.1377/hlthaff.2022.00520

[14] Shariq, S., Pinto, A., Budhathoki, S., Miller, M., and Cro, S. (2023). Barriers and facilitators to the recruitment of disabled people to clinical trials: A scoping review. *Trials, 24(1)*. doi: 10.1186/s13063-023-07142-1

inclusion of diverse populations in clinical trials, the FDA underscores that diversity is not a superficial requirement but a fundamental aspect of scientific integrity and public health.

The draft guidance's emphasis on developing and implementing DAPs is particularly important given the historical context of clinical research, where marginalized groups have often been excluded or underrepresented. This exclusion has contributed to health disparities and has limited the medical community's understanding of how different populations respond to treatments. By addressing this issue directly, the guidance ensures that future clinical trials are designed with diversity in mind from the outset.

Furthermore, the draft guidance recognizes that diversity extends beyond race and ethnicity, encompassing factors such as age, disability, sex, gender identity, sexual orientation, and socioeconomic status.[15] The NHC commends the FDA for recognizing the extent of diversity, which is crucial for capturing the full range of human variability and ensuring that clinical research is inclusive of all segments of the population.

Structured Approach to Enrollment Goals

The NHC appreciates the structured approach to setting enrollment goals, which are disaggregated by race, ethnicity, sex, and age group to promote inclusivity. This method not only requires the inclusion of diverse populations in clinical trials but also ensures that sponsors set specific, measurable goals grounded in data sources such as registries and epidemiological surveys where available. This data-driven foundation enables sponsors to establish realistic and achievable enrollment goals that reflect the prevalence of the disease or condition being studied.

This emphasis on data-driven goal setting represents an improvement over previous approaches, where diversity efforts often faltered due to a lack of clear targets and an absence of a structured framework. The draft guidance addresses these shortcomings by providing sponsors with tools to develop robust and evidence-based DAPs. Providing illustrative examples of DAPs disaggregated by categories—especially those not commonly utilized by sponsors previously—would further support these efforts. This structured approach enhances the inclusivity of clinical trials, ensuring that the data collected is more representative of the populations who will ultimately benefit from the medical products being tested.

Moreover, by encouraging sponsors to consider the unique challenges and barriers that different populations may face in accessing clinical trials, the draft guidance supports the development of more effective strategies for reaching underrepresented groups. This comprehensive approach to enrollment goals is a crucial element in promoting diversity in clinical trials and is expected to lead to more equitable health outcomes

Community Engagement and Cultural Competency

[15] Schoch, S. (2023). Patients, poverty, and participation in research: The hidden costs of disease and socioeconomic status. Retrieved from https://nationalhealthcouncil.org/blog/patients-poverty-and-participation-in-research-the-hidden-costs-of-disease-and-socioeconomic-status/

The NHC appreciates the draft guidance's emphasis on community engagement and cultural competency training for investigators. Building trust with underrepresented populations is essential for improving participation in clinical trials, and the draft guidance recognizes that this trust is often best earned through sustained engagement with communities.[16] By encouraging sponsors to partner with community organizations, engage with local leaders, and tailor their outreach efforts to the needs of specific populations, the draft guidance provides a roadmap for building stronger relationships with the communities that clinical trials aim to serve.

Cultural competency training is also a critical component of this effort. Investigators and clinical trial staff need to understand the cultural and social factors that may influence a person's decision to participate in a clinical trial. This includes being aware of historical injustices that may have contributed to mistrust in the medical system and understanding the unique needs and concerns of different communities. The draft guidance emphasizes the importance of this training, ensuring that clinical trial staff are equipped with the knowledge and skills they need to effectively communicate with and support diverse participants.

Additionally, public education is crucial for increasing diversity in clinical trials, as myths and misconceptions about clinical research can deter participation, particularly among underrepresented populations. The FDA could support educational initiatives that dispel these myths and provide clear, accurate information on the importance of diverse participation in clinical research. These efforts could include public awareness campaigns, community-based education programs, and partnerships with patient organizations. Developing culturally relevant educational materials—such as brochures, videos, and online resources that explain the benefits of clinical trial participation and address common concerns—would enhance outreach efforts. To further improve their effectiveness, these materials should be designed with input from diverse communities, available in multiple languages, and accessible to individuals with disabilities, ensuring they resonate with and reach all intended audiences.

These elements of community engagement, cultural competency, and public education are essential for the success of DAPs. Without them, efforts to recruit and retain diverse participants are likely to fall short. The draft guidance's focus on these areas reflects an understanding of the challenges involved in promoting diversity in clinical trials and provides sponsors with the tools they need to overcome these challenges.

Opportunities to Strengthen and Clarify the Draft Guidance

While the NHC supports the overall direction of the draft guidance, there are several areas where additional clarification and guidance would be beneficial. These areas include the applicability of DAPs to ongoing trials, the setting of enrollment goals, and the inclusion of rare diseases. Addressing these issues will help ensure the guidance is as effective and comprehensive as possible.

[16] Clark, L. (2021). Achieving diversity in clinical research: A continuing challenge for sponsors, investigators and communities. Retrieved from https://nationalhealthcouncil.org/blog/achieving-diversity-in-clinical-research-a-continuing-challenge-for-sponsors-investigators-and-communities/

Clarification on the Applicability to Ongoing Research and Development

While the draft guidance specifies that DAP requirements apply to clinical trials for which enrollment begins 180 days after the final guidance is published, there remain concerns about how DAPs should be integrated into ongoing clinical trials or development programs that may not fall directly under the statutory requirements. Sponsors working on trials in earlier phases, or those nearing pivotal trials but not yet enrolling, may face uncertainty on how best to implement DAPs in line with future requirements. For example, some sponsors may seek to incorporate diversity efforts in earlier-stage trials (e.g., Phase 2) to ensure alignment with future Phase 3 DAP requirements but are unclear about how the FDA will evaluate or guide these efforts. Others may face logistical challenges in ongoing trials that are close to enrollment but were planned before the final DAP guidance, raising questions about the impact on IRB approvals, budgeting, and participant recruitment. The NHC encourages the FDA to provide clarification on how DAPs should be applied across different stages of development and to clarify how diversity data from earlier phases may inform later trial requirements. Additionally, we recommend that the FDA develop practical, flexible solutions to help sponsors navigate these challenges while maintaining trial continuity and ensuring diversity goals are effectively embedded throughout the clinical research process.

Clarification on Setting Goals and the FDA's Role

The draft guidance would benefit from more detailed instructions on setting enrollment goals based on prevalence data, along with clear criteria for how the FDA will evaluate and guide these goals. While the guidance provides a general framework, it lacks specific direction on calibrating these goals to accurately reflect disease prevalence across different demographic groups. The NHC recommends that the FDA offer additional clarity, including examples of how to calculate prevalence for various populations and how to adjust goals based on factors such as disease severity, treatment availability, and population size. Clear, data-driven methods will help ensure that enrollment goals are realistic, achievable, and aligned with the overall objectives of promoting diversity in clinical trials.

Monitoring and Reporting on DAPs

A structured mechanism to track and assess the progress of sponsors in meeting diversity goals is essential to the success of DAPs. The NHC recommends making regular reporting from sponsors a core component of the DAP framework, where sponsors provide consistent updates on their progress toward meeting enrollment goals. Notably, Section 3604 of the Food and Drug Omnibus Reform Act requires the FDA to submit an annual summary report to Congress, which must also be made publicly available, detailing the progress made toward increasing diversity in clinical studies. For this reporting to be effective, the FDA should provide more clarity on the process for submitting DAPs, including guidance on when revisions or updates are required, and the process for submitting modified DAPs. Clarification in these areas would allow sponsors to proactively manage and update their diversity plans throughout

the course of a trial, ensuring alignment with evolving study needs and goals. This reporting process will provide the FDA, Congress, and the public with valuable insights into the efforts to meet diversity targets, while enhancing transparency and allowing for a clear assessment of overall industry progress.[17] Additionally, these reports can help identify areas where improvements are needed to ensure continued advancement.

To optimize this statutorily required reporting process, the NHC suggests that sponsors and clinical research organizations assume primary responsibility for implementing site-level oversight and monitoring, utilizing their existing resources. By leveraging their resources and expertise, sponsors can support progress without adding unnecessary complexity, while still providing the FDA with the necessary data to assess industry-wide improvements in diversity efforts.

Considerations for Rare Diseases

The NHC appreciates the draft guidance's recognition of the unique challenges involved in enrolling diverse populations for rare disease trials. Rare diseases often have small and geographically dispersed patient populations, making it especially difficult to achieve diversity in clinical trials. While the draft guidance acknowledges these challenges, it offers limited specific solutions for addressing them, and more detailed guidance is needed to help sponsors conduct inclusive and representative trials for rare diseases.

Given the small size and fragmented nature of rare disease populations, traditional methods of calculating prevalence may not always be applicable or reliable. For some conditions that do not technically fall under the rare disease category but still face similar challenges, such as limited demographic data, setting appropriate enrollment goals can be particularly complex. The FDA should provide alternative methods for estimating prevalence when standard data is insufficient and outline flexible approaches for setting enrollment goals that reflect these unique challenges. These methods might include leveraging patient registries, collaborating with patient organizations, and using innovative trial designs that accommodate small and dispersed populations.

The NHC also supports allowing high-level diversity goals and general reporting for small trials, as detailed demographic data could risk unblinding study results, particularly in rare disease studies. In such cases, high-level reporting would protect study integrity while maintaining transparency. The FDA should clarify how sponsors should handle updates to DAPs in their annual reports when there are risks associated with sharing specific data.

Accessibility to studies and trial sites remains a critical factor for rare disease populations, who often face significant logistical challenges in accessing trial locations. The FDA should consider providing more specific guidance on improving accessibility, including through decentralized trials, telehealth options, or mobile trial units, to ensure broad participation.

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[17] Food and Drug Omnibus Reform Act, H.R. 2617, 117th Congress. (2022). https://www.congress.gov/117/bills/hr2617/BILLS-117hr2617enr.pdf

Finally, there is a need for flexibility in setting and achieving diversity goals for rare diseases. The FDA should offer guidance on balancing the need for diversity with the practical challenges inherent in these trials, including mechanisms for requesting waivers or modifications to DAPs when appropriate. Further discussion on the unique aspects of rare disease drug development, the associated challenges, and when waivers may be warranted would greatly benefit all stakeholders, including sponsors, patient organizations, clinical researchers, and regulators.

Guidance on Periodic Review and Updates

The draft guidance would benefit from a mechanism for periodic review and updates to ensure that it remains relevant and effective as the landscape of clinical research evolves. The field of clinical research is constantly changing, with new technologies, methodologies, and patient populations emerging over time. To keep pace with these changes, the guidance must be regularly reviewed and updated to reflect the latest advancements and best practices in clinical trial diversity.

A mechanism for periodic review could involve the establishment of an advisory committee or working group that includes representatives from the FDA, industry, academia, and patient organizations. This group should be balanced and reflective of both chronic and rare disease representation, ensuring that the unique challenges faced by both groups are considered in the development of clinical trial policies. Such a diverse committee would be tasked with monitoring developments in the field and recommending updates to the guidance as needed, helping ensure that the guidance remains responsive to all stakeholders' needs.

In addition to periodic reviews, the FDA could also consider incorporating a feedback mechanism into the guidance. This would allow sponsors and other stakeholders to provide ongoing input on the effectiveness of the guidance and suggest areas for improvement. This continuous feedback process would be valuable for identifying emerging challenges and opportunities in clinical trial diversity, ensuring that the guidance evolves in response to these developments.

Cultural and Educational Adaptability

The NHC strongly supports the inclusion of culturally adaptable information and educational initiatives in the draft guidance. Effective communication with diverse populations is essential for ensuring that all individuals can participate in clinical trials. However, reaching these populations requires more than mere translation of materials into language other than English; it requires a comprehensive understanding of the cultural and social factors that shape individuals’ perceptions of and engagement with clinical research.

The draft guidance recognizes the importance of cultural competency but could go further in providing specific recommendations for how sponsors can tailor their communication and outreach efforts to meet the needs of diverse communities. This could include guidance on conducting community-based participatory research, developing culturally relevant messaging, and engaging with community leaders and organizations that have the trust of the target population. By providing more detailed

guidance in this area, the FDA can help sponsors develop more effective strategies for recruiting and retaining diverse participants.

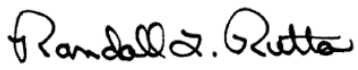
In addition to cultural adaptability, the draft guidance should also address health literacy. Many individuals, particularly those from underrepresented populations, may have limited health literacy, which can hinder their ability to comprehend complex medical information and make informed decisions regarding participation in clinical trials.[18] The FDA should provide guidance on how sponsors can assess the health literacy of their target populations and develop materials that are accessible and easy to understand. This could include the use of plain language, visual aids, and interactive tools that help convey key information in a clear and engaging way.

Conclusion

The NHC commends the FDA for its leadership in promoting diversity in clinical trials. This draft guidance represents a positive step toward more inclusive and representative clinical research. While we strongly support the overall direction of the guidance, we believe that there are several areas where additional clarification and guidance would be beneficial. By addressing these issues and providing additional support to sponsors, the FDA can help to ensure that the goals of the guidance are achieved and that all populations are adequately represented in clinical research.

The NHC appreciates the opportunity to provide input on this important guidance and looks forward to continued collaboration with the FDA to advance patient-centered health policies. Please do not hesitate to contact Eric Gascho, Senior Vice President, Policy and Government Affairs, at egascho@nhcouncil.org or Omar Escontrías, DrPH, MPH, Senior Vice President, Equity, Research and Programs at oescontrias@nhcouncil.org if you or your staff would like to discuss these comments in greater detail.

Sincerely,



Randall L. Rutta
Chief Executive Officer

[18] National Health Council. (2021). Health literacy: A three-part series to support better communication. Retrieved from https://nationalhealthcouncil.org/education/health-literacy/