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Via Electronic Delivery

Robert M. Califf M.D
Commissioner
U.S. Food and Drug Administration
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10903 New Hampshire Avenue
Building 66, Room 5431
Silver Spring, Maryland 20993-0002

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials: Guidance for Industry [Docket No. FDA-2021-D-0789]

On behalf of patients and families impacted by rare diseases, the EveryLife Foundation for Rare Diseases is pleased to offer the following comments to inform the U.S. Food and Drug Administration on the Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials.

The EveryLife Foundation for Rare Diseases is a 501 (c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures. EveryLife's establishment of a diverse alliance comprised of patient advocacy organizations, industry leaders, coalition groups, and other relevant stakeholders guides our policy efforts and provides advice and insight on urgent policy issues impacting the rare disease community. We are grateful for the opportunity to engage in policy conversations to improve clinical trial diversity and to offer input that reflects our community's commitment to diversity, equity, inclusion, and accessibility (DEIA).

The most recent estimates suggest that there are over 7,000 rare diseases. While most rare diseases (93-95%) lack any FDA-approved disease-modifying therapies, we are grateful for recent breakthroughs that have extended the life expectancies of once-fatal conditions and we are optimistic about the research that is ongoing to develop treatments for additional conditions. Remarkable success in clinical trials and studies brings opportunity for further

improvement. The need for diversity and inclusion in clinical trial participation and data collection is significant.

The 2020 FDA Drug Trials Snapshots Summary Report noted that CDER (Center for Drug Evaluation and Research) approved 53 novel drugs from January 1, 2020-December 31, 2020, either as new molecular entities (NMEs) or as new therapeutic biologics. The participation percentages for clinical trials varied significantly by subpopulation with 75% of those taking part being White, 11% Hispanic, 8% Black or African American, and 6% Asian. Over the past few years, we have seen an upward trajectory in the percentage of drugs to treat rare or "orphan" diseases. While a monumental achievement, it is time to include diverse participants in the drug development process.

A study led by Turner et al. (2022) investigated two decades worth of data from over 20,000 clinical trials and examined changes over time. The researchers found that less than 44 percent of trials reported any race or ethnicity data, a percentage that is steadily improving over time. Among the 8,871 trials that did report race or ethnicity data, minorities were significantly underrepresented.

It is essential that diversity plans be created for medical devices, diagnostic, and drug/biologic development. According to the Sjoding et al. (2020) study, Black patients had approximately three times the frequency of occult hypoxemia that was not detected by pulse oximetry as White patients. The mdgroup (2020) pointed out that when it comes to drug/biologic inequities, doctors are likely to diagnose conditions or prescribe medication that is effective for individuals with European genes, but not nearly effective for people of other races and ethnicities.

To ensure that all communities benefit from scientific advances, it is essential that clinical trials include people with diverse lived experiences and living conditions. The historical lack of diversity and inclusion in clinical trials has created gaps in our understanding of diseases and conditions, disease prevalence, diagnostic timelines, preventative measures, and treatment efficacy across populations. These gaps have contributed to worse health outcomes for marginalized communities, demonstrating the need for meaningful representation of diverse participants in clinical trials. Further exacerbating the inequities in participation is the number of rare diseases that are small in population size. We urge the FDA to consider these factors and ensure the appropriate amount of flexibility and accountability where warranted.

We commend the FDA for recognizing the tradeoff between greater diversity standards and expedited development and approval of medical products as it relates to rare and life-threatening conditions. Establishing approaches that generate data from broader and more diverse populations early during the development phase is crucial to ensuring that the product is safe and effective for every patient.

We applaud the FDA for issuing past and current guidance that recommends approaches that sponsors of clinical trials can utilize to increase enrollment of underrepresented populations.

The rapid improvement of race and ethnicity data in clinical trials and surveillance are because the FDA and Congress have recognized the need and benefits of diverse participation to advance therapies relevant to the general population and the rare disease community. The EveryLife Foundation is pleased to see our DEIA priorities reflected in these recommendations. We encourage the agency to work towards further refinement of these recommendations to activate participation for all marginalized populations.

Opportunities for DEIA training

In addition to comments submitted by the National Health Council (NHC) and supported by the EveryLife Foundation, we urge you to improve research team demographics. A reflection of the community being served will influence diverse participation in clinical trials. Further, we recommend that the plan include information regarding the establishment of education and training programs for clinical trials conductors with respect to DEIA.

Opportunities for guidance on decentralized clinical trials

We would also encourage the agency to provide additional information regarding the development and implementation of decentralized clinical trials as it relates to marginalized group participation. These recommendations will guide study design and provide increased understanding of similarities and/or differences in the disease or condition under study that are associated with the underrepresented racial and ethnic populations in the United States.

Opportunities to create plan of action for reducing burden of participation

We applaud FDA's acknowledgment of stakeholder's recommendations regarding a sponsor-developed plan that identifies the operational measures that will be implemented to improve safety and effectiveness of a drug, product, or device through increased diversity in clinical trials. While we recognize these efforts, we encourage the development of an FDA-guided plan of action discussing financial reimbursement for expenses incurred by participation in a clinical trial or study.

Underserved populations often do not participate due to logistical challenges, financial burdens, and distrust in the medical system. A lack of complete knowledge of the natural history of a rare disease/condition or diverse demographic subgroup is caused by the limited medical specialists who have diagnosed and treated a small number of patients with rare diseases (Bollerman, 2020). The limited number of rare disease experts and sites influence the number of patients who may be enrolled in clinical trials. Credevo (2021) addressed three main challenges that rare disease clinical trials face: 1) finding sites that have experience with trials specific to rare conditions; 2) continuous engagement of sites for retention of patients for a longer duration; and 3) a limited number of research sites complementary to patient locations. Due to long distances from clinical research sites, rural residents find it difficult to participate in clinical trials or studies. For rare disease patients and families, the limited number of clinical and scientific experts and limited clinical trial sites for a given program, often mean days or weeks of missed work, expensive travel arrangements and additional supportive care costs that

are mostly uncovered by existing renumeration opportunities. A lack of participation is also linked to financial barriers such as low incomes, a lack of insurance coverage, inflexible work schedules, and the cost of childcare. Remuneration should also extend to the caregivers who provide direct care to the patient. In certain instances, patient participation is contingent on the caregiver's ability to provide transportation to research sites, administer medication, and collect necessary data.

Opportunities for outreach and education strategies

We commend the FDA for briefly providing trial and enrollment retention recommendations through sustained community engagement. We would like to see the agency include recommendations for sponsors on how to initiate outreach and maintain relationships with community-based organizations and community leaders. There is a need to consider learning about the various formal and informal patient advocacy organizations, their missions, key programs, existing resources, and staffing levels prior to engaging with the community. We recommend sponsors meet patients and advocacy leaders where they are and help increase knowledge and trust in the therapy development process.

Furthermore, we suggest that patient-focused drug development workshops utilize a DEIA plan that emphasizes intentional engagement with marginalized communities. Whenever 'best practices' are established, we recommend FDA patient affairs staff and/or ARC hold a yearly public workshop so that others can benefit from these learnings.

We would also encourage the FDA to create recommendations for sponsors regarding the creation of an annual report discussing the outreach progress being made toward increasing the diversity of clinical trials and enrollments in studies. Further, we recommend including in this plan information on why sponsors can or cannot implement less burdensome follow-up requirements for trials participants.

Opportunities to expand equity and inclusion

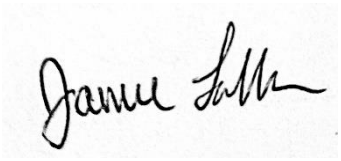
In addition to comments submitted by the NHC and supported by the EveryLife Foundation, we urge you to focus future efforts on the engagement and retention of other underrepresented communities in the United States. This includes issuing guidelines that encourage the participation of people from the LGBTQIA+ community, multiple geographical locations, diverse socioeconomic statuses, pregnant and lactating women, immigrants, and more.

Conclusion

The EveryLife Foundation is pleased by the FDA draft guidance on clinical trial diversity. We are grateful to all the community members who have worked tirelessly to ensure that the needs, priorities, opportunities, and urgency of our underrepresented rare disease community is strongly reflected in these recommendations. The foundation and its partners are eager to continue to weigh in and work with the agency, sponsors, and patient communities to ensure that the diverse rare disease communities' patient experience continues to inform recommendations and decision-making all throughout the product development life cycle.

Thank you for the opportunity to provide comments on the Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials. If we can provide additional information to support your process, please contact Jamie Sullivan, Senior Director of Policy at jsullivan@everylifefoundation.org.

Sincerely,



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