September 19, 2025

Dr. Martin Makary

Commissioner

Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993

RE: FDA Guidance for Industry: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies, Docket: FDA-2025-D-1797

The Rare Disease Diversity Coalition (RDDC) appreciates the opportunity to provide comments on FDA's draft guidance on the Inclusion of Pregnant and Breastfeeding Women in Clinical Trials (E21). We commend FDA for recognizing the longstanding gap in evidence for pregnant and breastfeeding women, a gap that has limited clinical decision-making and compromised equitable health outcomes.

As an advocacy group dedicated to advancing equity for patients with rare diseases, we recognize the pivotal role that inclusive clinical trial enrollment plays in advancing medical research and improving health outcomes. The draft guidance marks an important shift away from the presumptive exclusion of these populations and toward building a more inclusive evidence base that can support safe and effective treatment decisions. RDDC urges FDA to strengthen the guidance by explicitly recognizing the unique needs of pregnant and breastfeeding women living with rare diseases and of women from underrepresented racial, ethnic, and socioeconomic groups who continue to face disproportionate barriers to trial participation. By strengthening the guidance in this way, FDA can ensure that representation priorities reflect the reality of those most often excluded.

I. About RDDC

RDDC, a partnership involving rare disease and equity advocates, public health experts, and industry leaders, was launched in 2020 to address the extraordinary challenges faced by rare disease patients of color. RDDC is focused on reducing health disparities in the rare disease community. We do this by developing and deploying an evidence-based suite of advocacy tools and research interventions that will provide tangible solutions for rare diseases. Our work is rooted in a commitment to improving the lives and health outcomes of rare disease patients from patients across different backgrounds and communities in the United States and globally.

II. RDDC's Comments on the Draft Guidance

A. Explicitly Recognize the Importance of Rare Disease Populations in Clinical Trials

We recommend that the FDA explicitly acknowledge the importance of including pregnant and breastfeeding women with rare diseases in clinical trials. Rare diseases remain among the highest unmet medical needs, with approximately 80 percent genetic in origin and often present at birth.[1] Many women live with these conditions into their reproductive years, where pregnancy and breastfeeding can significantly affect disease management. Despite this reality, systematic data on treatment safety and effectiveness in these populations is almost entirely absent.

By affirming the role of rare disease patients in this guidance, FDA can help ensure that clinical research reflects the experiences of those who face the most uncertainty in care. Inclusion would also generate data on the progression of rare conditions during pregnancy, the safety of continuing or discontinuing treatment, and the impact on maternal and fetal outcomes. Such evidence would be invaluable for clinicians, patients, and families making critical treatment decisions. Recognizing rare diseases in this guidance signals FDA's commitment to equitable evidence generation for all populations, including those often overlooked in the research process.

B. Emphasize Increase Underrepresented Population Enrollment

We recommend that FDA highlight increasing the inclusion of underrepresented populations in clinical trials as a core priorities in implementing this guidance. Women of color remain significantly underrepresented in clinical research, with Black and Hispanic patients accounting for less than 15 percent of trial participants despite comprising nearly 35 percent of the U.S. population.[2] For rare diseases, this problem is compounded by delayed diagnoses and systemic factors that further exclude minority women from trial opportunities.

Explicitly linking this guidance to FDA's broader clinical trial diversity goals will reinforce the importance of ensuring pregnant and breastfeeding women from all backgrounds are represented. Doing so not only addresses fairness but also improves the quality and relevance of trial results. Treatments studied in homogeneous populations often fail to capture important safety or

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[1] National Stem Cell Foundation, Rare Childhood Diseases (2025), *accessible at*: https://nationalstemcellfoundation.org/focus/rare-childhood-diseases/

[2] National Library of Medicine, Race/Ethnicity Reporting and Representation in US Clinical Trials (2020).

effectiveness differences across groups, weakening their real-world applicability. By encouraging sponsors to incorporate diversity planning into their trial designs, FDA can help ensure that this effort to expand inclusion truly reaches those most often left out.

C. Address the Clinical Implications of Rare Disease Management During Pregnancy and Breastfeeding

We recommend that FDA strengthen the guidance by acknowledging the unique clinical implications of managing rare diseases during pregnancy and breastfeeding. Pregnancy can alter disease trajectories, affect drug metabolism, and complicate treatment decisions in ways that remain poorly understood. Some rare diseases may worsen due to increased stress on the body, while others may temporarily improve due to immune system suppression. However, the lack of research on rare diseases in pregnancy often leaves women and their healthcare providers without clear guidelines. Medications that are effective for disease management may pose risks to fetal development, forcing women to choose between controlling their symptoms and ensuring a healthy pregnancy.[3] Without evidence drawn from real-world trial participation, both patients and clinicians are left to make decisions in the dark.

Incorporating this perspective into the guidance would encourage sponsors to design studies that specifically examine these dynamics. Such trials could provide essential data on dosage adjustments, maternal health outcomes, and the long-term well-being of infants exposed to treatment in utero or through breastfeeding. By highlighting these considerations, FDA meaningfully improve the safety and effectiveness of care for pregnant and breastfeeding women with rare conditions.

D. Encourage Proactive Recruitment and Retention Strategies for Pregnant and Breastfeeding Women

We recommend that FDA encourage sponsors to adopt proactive, patient-centered approaches to recruitment and retention of pregnant and breastfeeding women, particularly those with rare diseases. Recruitment is already challenging for rare conditions, given the small and dispersed patient populations. These challenges are magnified for pregnant and breastfeeding women, who face additional logistical and cultural barriers to trial participation.

Effective strategies must go beyond standard recruitment approaches. Sponsors should develop culturally and linguistically tailored trial materials, partner with trusted advocacy and community organizations, and design studies that reduce travel and time burdens, including through decentralized or hybrid models. These efforts not only expand participation but also build trust, which is essential for long-term engagement with underrepresented groups. In addition, sponsors should account for social determinants of health that often dictate whether a patient or caregiver can realistically participate in a clinical trial. For example, one caregiver shared that they agreed to enroll in a trial but had not realized the significant time commitment required, including multiple weekly visits that conflicted with their work schedule and childcare responsibilities. The

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[3] American Medical Women's Association, Women and Rare Disease, *accessible at*: https://www.amwa-doc.org/our-work/initiatives/rare-disease-awareness-campaign/#:~:text=Challenges%20During%20Pregnancy,expecting%20mothers%20with%20rare%20diseases.

out-of-pocket costs and disruption to family life would have been overwhelming, ultimately precluding them from particiapation. Stories like this highlight how non-medical burdens can act as barriers to participation and reinforce the need for trial designs that meaningfully address these realities. By calling attention to these strategies and considerations, FDA can help ensure that this guidance effectively translates into practical improvements in enrollment and retention.

Conclusion

Thank you for the opportunity to provide these comments. RDDC looks forward to working with the FDA to help achieve greater inclusion in clinical trials.

Sincerely,

Jenifer Waldrop

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