Fortrea

Achieving diversity in drug development programs for obesity

Contributors

Claudia Filozof, MD, PhD, Vice President, Therapeutic Area Head of Obesity, MASH and Hepatology Indications

Alicia Baker, DRSc, MS, EMBA, Head of Regulatory Strategy, Product Development & Market Access Consulting

Peter Alfinito, PhD, Executive Director, Strategy Delivery and Growth

Beatriz Rocha, MD, PhD, Chief Regulatory Liaison Officer

Understanding the importance of diversity in clinical trials

In an ideal world, the participants in a clinical trial would reflect the demographic characteristics of those who will use the medication in the real world. Reaching a study population that is representative of the intended population helps understand how a medicinal product affects people of different races and ethnicities, age and sex.

The past and even current disparities in clinical trial populations are well known. Consider the example of the inclusion of Black and Hispanic Americans in obesity trials. They represent 13% and 18% of the population, respectively. However, obesity prevalence is higher in these two groups, and they are disproportionately affected by the associated comorbidities.[1] Nevertheless, these populations are grossly underrepresented as participants in clinical trials. Sex differences in studies also differ, with females being significantly overrepresented as participants in weight-loss studies. The paucity of sex and racial/ethnic diversity in clinical research can lead to research findings that are not generalizable to the entire population.[2]

Lack of proper representation is due to a variety of reasons. Some barriers are related to the clinical trial itself, such as the design, eligibility, sites and long enrollment periods. Other factors are directly related to patients and the health system. Of relevance is the limited access to healthcare that is prevalent in this population as well as the lack of incentive for participating hospitals.

While the FDA has previously encouraged sponsors to include traditionally underrepresented demographic subgroups, the U.S. FDA's Omnibus Reform Act of 2022 (FDORA) was enacted in December 2022 and included provisions to promote diversity and inclusion in clinical trials.

To help sponsors reach their diversity goals throughout the regulatory process and trial execution, this white paper discusses the FDA's latest requirement for a Diversity Action Plan (DAP). Learn what to expect and how you can best support your Phase III or pivotal study equivalent clinical trials of new drugs or devices with registrational intent.

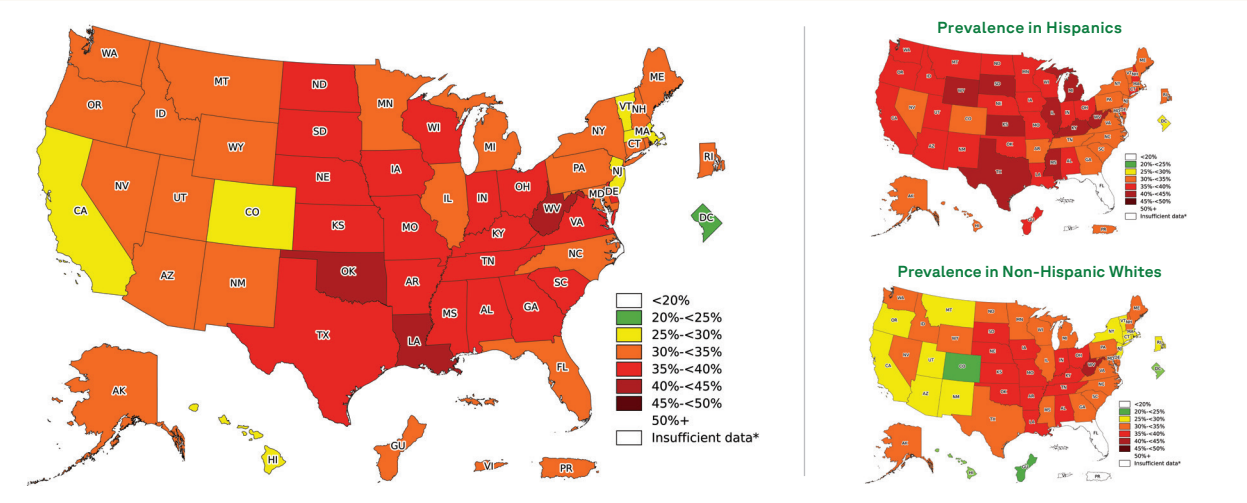
Obesity prevalence and trends in obesity-related mortality and racial disparities

Worldwide adult obesity prevalence has more than doubled since 1990, and adolescent obesity has quadrupled. From 1990 to 2022, the age-standardized prevalence of underweight among adults decreased in 129 countries (65%) for women and 149 (75%) for men. Age-standardized prevalence of obesity in adults increased from 1990 to 2022 in 188 countries (94%) for women and in all except one country for men.[3] The rise in obesity is surpassing the decline in underweight individuals.[4] There is a clear transition from underweight to obesity dominance in most low- and mid-income countries.

In the U.S., overall obesity prevalence in adults is 41.9%. However, significant disparities in the prevalence, complications, and treatment outcomes of obesity among Blacks and other racial or ethnic groups in the United States have been well-documented over time. Black and Latinos have the highest obesity rates (49.9% and 45.6%, respectively, in adults). Obesity rates are also increasing among children and adolescents and have tripled among this population since the mid-1970s. Black and Latino youth have higher rates than their white peers. There is also a steady increase in Asian and Pacific Islander people and people who identify as multiracial in the U.S. Single-race Asian groups had lower odds of obesity compared with White individuals when using standard BMI cutoffs. However, when applying Asian-specific BMI cutoffs, the prevalence of obesity among single-race Asian groups is similar to that among White individuals. Furthermore, obesity prevalence is higher among Pacific Islander groups compared with Asian groups and White individuals.[5]

Figure 1: Overall obesity prevalence in the U.S.

Source: Adult Obesity Prevalence Maps. U.S. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. (Sept. 21, 2023).



Finally, disparities in obesity care disproportionately impact racial and ethnic minorities mainly in Black individuals with obesity. Obesity-related conditions such as hypertension and pancreatic cancer and treatments for obesity-related diseases such as sleep apnea disproportionately affect racial/ethnic minorities. These disparities are most significant for Black Americans. Studies have found that while Black women have the highest rates of obesity, Black men have the highest mortality rates from obesity-related illnesses. Such disparities highlight the need to address the existing inequities in access and quality of obesity care.[6]

Following the progression of U.S. legislation leading to Diversity Action Plans

The FDA first published draft guidance in April 2022, which recommended that sponsors develop Diversity Action Plans (DAPs).[7] On December 29, 2022, legislation was passed, which contained several provisions to promote diversity in clinical trials, supporting the FDA's evaluation of safety and efficacy of new drugs and devices.[8] On June 26, 2024, the FDA issued a draft guidance relating to the format and content of DAPs,[9] which replaced the April 2022 guidance.

Under the Food and Drug Omnibus Reform Act of 2022 (FDORA), legislation requires DAPs to be submitted to Phase III, or any pivotal study in the U.S., of new drugs or medical devices and diagnostics that use the 510(k), premarket approval (PMA, *de novo* and investigational device exemption [IDE]), for which enrollment commences 180 days from the publication of the final guidance. As this is not yet the final guidance it did not trigger the 180-day timeline. However, a final guidance might be expected sooner rather than later after the 90-day public comment period.

Aligning with the FDA's current request for data on underrepresented populations

Since 2022, the FDA has asked sponsors to discuss their plans to ensure diversity and inclusion of underrepresented populations in pivotal clinical trials, and sponsors have been actively gathering the agency's feedback. The June 2024 guidance continues to promote an increase in enrollment of participants who are members of historically underrepresented populations in clinical and medical devices studies to help improve the strength and generalizability of the evidence for the intended use population.

In addition, it considers factors beyond what is required by FDORA (age, sex, racial and ethnic demographic characteristics) when developing enrollment goals—including geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy or lactation status, and comorbidities. Justification for proposed enrollment goals should be based on estimated prevalence or incidence of the disease in the intended US population.

It also specifically indicates that global clinical development programs should reflect enrollment goals for the entire study population and not be limited to US-enrolled participants and that a proportional representation is not needed in every clinical study, but such representation should be achieved in the totality of the clinical development program. A greater than proportional enrollment may be necessary in certain populations to elucidate potentially clinically important differences in responses between subsets of the study population.

The DAP should also describe the rationale for enrollment goals, including the methodology used to derive target enrollment goals, and the measures to meet the goals, including strategies for enrollment, retention, monitoring enrollment and mitigation to overcome barriers.

The DAP should be submitted to the IND no later than when the protocol is submitted to the FDA for a Phase III or other registrational study and applies to pediatric and rare diseases. For medical devices, the DAP should be included in IDE application or, as appropriate, any premarket notification, request for classification, or application for premarket approval.

Feedback on the DAP (initial or revised) is at the FDA's initiative; sponsors with specific questions may include these as a topic for discussion in meetings with the FDA.

Finally, if the inclusion of a certain population is impractical or unreasonable, the sponsor can submit an official waiver request no later than 60 days before the DAP required submission. The FDA may grant a full or partial waiver from the requirement to submit a DPA, but these are likely to be granted only in "rare instances."

Understanding recommendations versus requirements

Interestingly, while in general FDA's guidance documents do not establish legally enforceable responsibilities and are seen as recommendations as per the use of the word should, an exception to this framework derives from the requirement in section 3601 of FDORA for FDA to specify in guidance, the form and manner for the submission of the DAPs it will have binding effect, once this guidance is finalized, as indicated by the use of words *must*, *shall* or *required* (see section VII of the guidance).

Our role in promoting diversity in clinical trials

At Fortrea, we're committed to helping sponsors increase the diverse representation of populations in their clinical trials. Our Diversity in Clinical Trials Multifunctional Workstream and Advisory Board oversee a complete and integrated solution across our Consulting and Clinical Operations services that provides the appropriate framework for success under an Integrated Research Organization (IRO) strategy.

From protocol development to study close, we offer an innovative and comprehensive diversity solution that encompasses:

- DAP: Write, submit and engage with regulators and support the final report writing and submission
- Incorporate the Voice of Patient to understand patients' needs, support protocol optimization and capture feedback at the close of the study to continually improve the DAP design
- Assess the impact and track progress toward study enrollment goals (and potentially identify safety signals) with a real-time dashboard
- Perform corrective actions and adjust enrollment and retention strategies based on findings presented in the dashboard

Additionally, a comprehensive, multi-faceted, strategic operational approach is needed to ensure diversity targets are met in obesity trials. This approach may include (but is not limited to) the following:

- **Pre-identification of a population:** Due to the rapid enrollment of obesity studies, pre-identification of a diverse patient population is needed to ensure diversity while maintaining fast enrollment
- **Strategic site selection:** Appropriate site selection can ensure sites have dieticians who can meet the needs of the patient populations being recruited

- **Investigator selection:** Including obesity investigators from underrepresented populations, as it has been demonstrated that underrepresented participants are more likely to enter clinical trials where the investigators are from similar racial and/or ethnic backgrounds
- **Targeted training:** Through training, trial teams should understand the importance and rationale of participation from diverse groups in clinical trials and explore barriers, which may require mitigation, at the site and investigator level
- **Feasibility outreach questions:** The importance of diversity at the site level can be highlighted through specific feasibility outreach questions, such as: "Does your institution have a process or initiative to increase patient diversity in the clinical trials in which you participate?" and "Does your institution track recruitment of diverse patient populations?"
- **Patient advocacy group outreach:** Engage patient advocacy groups to promote awareness to specific populations in a format most likely to be successful for those patients
- **Targeted patient communications:** Develop targeted multimedia approaches to reach specific populations in a way that speaks directly to each group

Together with our sponsors, learn how we're advancing our shared goals to bring clinical research closer to all.

References

1. Centers for Disease Control and Prevention. Adult Obesity Facts. https://www.cdc.gov/obesity/php/data-research/adult-obesity-facts.html. Accessed May 7, 2024.
2. Johnson-Mann CN, Cupka JS, Ro A, et al. A Systematic Review on Participant Diversity in Clinical Trials-Have We Made Progr ess for the Management of Obesity and Its Metabolic Sequelae in Diet, Drug, and Surgical Trials. *J Racial Ethn Health Disparities*. 2023 Dec;10(6):3140-3149.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet*. 2024 Mar 16;403(10431):1027-1050.
4. Tumas, N. Double burden of underweight and obesity: insights from new global evidence. *The Lancet*. 2024 March 16;403(10431):998-999.
5. Bacong AM, Gibbs SL, Rosales AG, et al. Obesity Disparities Among Adult Single-Race and Multiracial Asian and Pacific Islander Populations. *JAMA Netw Open*. 2024;7(3):e240734.
6. Washington TB, Johnson VR, Kendrick K, Ibrahim AA, Tu L, Sun K, Stanford FC. Disparities in Access and Quality of Obesity Care. *Gastroenterol Clin North Am*. 2023 Jun;52(2):429-441.
7. U.S. Food and Drug Administration. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials; draft guidance for industry 2022. https://www.fda.gov/media/157635/download. Accessed May 7, 2024.
8. 117th Congress (2021-2022). **H.R.7667 - Food and Drug Amendments of 2022**. https://www.congress.gov/bill/117th-congress/house-bill/7667. Accessed July 1, 2024.
9. U.S. Food and Drug Administration. Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies; draft guidance for industry, June 2024. https://www.fda.gov/media/179593/download. Accessed July 1, 2024.

LEARN MORE at fortrea.com

Fortrea